Environment Canada | Environnement Canada
Health Canada | Santé Canada

Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

2-Butoxyethanol

Canada

Canadian Cataloguing in Publication Data

Priority Substances List Assessment Report : 2-Buthoxyethanol

(Priority substances list assessment report)
Issued also in French under title: *Liste des substances d'intérêt prioritaire, 2-Buthoxyethanol.*
At head of title: *Canadian Environmental Protection Act, 1999.*
Co-published by Health Canada.
Includes bibliographical references.
ISBN 0-662-33597-X
Cat. no. En40-215/66E

1. Buthoxyethanol – Toxicology – Canada.
2. Buthoxyethanol – Environmental aspects – Canada.
3. Environmental monitoring – Canada.
I. Canada. Environment Canada.
II. Canada. Health Canada.
III. Series.

TD196.E83P74 363.738'4 C2003-980073-3

Additional information can be obtained at Environment Canada's Web site at www.ec.gc.ca or at the Inquiry Centre at 1-800-668-6767.

© Her Majesty the Queen in Right of Canada (Environment Canada) 2003

Environment Canada | Environnement Canada
Health Canada | Santé Canada

Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

2-Butoxyethanol

Addendum

August 2003

Canada

ADDENDUM

A cut-off date for consideration of relevant data is specified in Assessment Reports on all Priority Substances to ensure the full evaluation of identified information through several stages of internal and external review. Information submitted following the cut-off date is considered primarily in the context of its implications for risk management or in setting priorities for conducting full reassessments at a later date.

For 2-butoxyethanol, Health Canada is pleased to acknowledge the results of additional research conducted in the period following the cut-off date for review specified in the Introduction to the Assessment Report. Preliminary review of more recent relevant published information referenced here, indicates that it potentially impacts on several areas of uncertainty delineated in this report but does not appreciably shift the weight of evidence in relation to the critical endpoint (i.e., haemolysis). Rather, it further supports the adoption in the assessment of a chemical specific adjustment factor in development of a Tolerable Concentration for this endpoint, which acknowledges quantitatively the considerable interspecies differences in sensitivity between rodents and humans to haemolysis following exposure to 2-BE (Udden, 2000, 2002).

Likewise, based on preliminary review, more recent information on potential modes of action for other effects, including those in the forestomach and liver of experimental animals, supports the lack of emphasis on these endpoints as a basis for essential conclusion in the Assessment Report (Green *et al.*, 2002; Park *et al.*, 2002a,b; Poet *et al.*, 2003; Siesky *et al.*, 2002).

These more recent data are being considered more fully in the preparation of a Concise International Chemical Assessment Document on 2-butoxyethanol by the International Programme on Chemical Safety. The output of this evaluation will be taken into account in the risk management phase under CEPA for this compound.

Also, in order to address a critical area of uncertainty indicated in the Assessment Report, further information on the presence and proportion of 2-butoxyethanol in consumer products currently available in Canada has been acquired subsequent to the cut-off date (ToxEcology, 2003). This information supports development of a much broader range of estimates of exposure and supports the degree of conservatism in the Assessment Report in which estimates of short term exposure from a small number of products are compared with the Tolerable Concentration.

Published Data on 2-Butoxyethanol Identified Subsequent to Cut-Off Date

Ghanayem B.I., S.M. Ward, B. Chanas, A. Nyska (2000). Comparison of the acute hematotoxicity of 2-butoxyethanol in male and female F344 rats. Human & Experimental Toxicology, 19: 185-192.

Green T., A. Toghill, R. Lee, R. Moore, J. Foster (2002). The development of forestomach tumours in the mouse following exposure to 2-butoxyethanol by inhalation: studies on the mode of action and relevance to humans. Toxicology, 180: 257-273.

Gualtieri J.F., M.D. DeBoer, C.R. Harris, R. Corley (2003). Repeated ingestion of 2-butoxyethanol: case report and literature review. Journal of Toxicology and Clinical Toxicology, 41(1): 57-62.

Jones K., J. Cocker, L.J. Dodd, I. Fraser (2003). Factors affecting the extent of dermal absorption of solvent vapours: a human volunteer study. Annals of Occupational Hygiene, 47: 145-150.

McKinney P.E., R.B. Palmer, W. Blackwell, B.E. Benson (2000). Butoxyethanol ingestion with prolonged hyperchloremic metabolic acidosis treated with ethanol therapy. Clinical Toxicology, 38(7): 787-793.

Park J., L.M. Kamendulis, J.E. Klaunig (2002a). Effects of 2-butoxyethanol on hepatic oxidative damage. Toxicology Letters 126: 19-29.

Park J., L.M. Kamendulis, J.E. Klaunig (2002b). Mechanisms of 2-butoxyethanol carcinogenicity: studies on Syrian hamster Embryo (SHE) cell transformation. Toxicological Sciences 68: 43-50.

Poet T.S., J.J. Soelberg, K.K. Weitz, T.J. Mast, R.A. Miller, B.D. Thrall, R.A. Corley (2003). Mode of action and pharmacokinetic studies of 2-butoxyethanol in the mouse with an emphasis on forestomach dosimetry. Toxicological Sciences, 71: 176-189.

Siesky A.M., L.M. Kamendulis, J.E. Klaunig (2002). Hepatic effects of 2-butoxyethanol in rodents. Toxicological Sciences, 70: 252-260.

Singh P., S. Zhao, B.L. Baylock (2001). Topical exposure to 2-butoxyethanol alters immune responses in female BALB/c mice. International Journal of Toxicology, 20: 383-390.

Singh P., B. Morris, S. Zhao, B.L. Baylock (2002). Suppression of the contact hypersensitivity response following topical exposure to 2-butoxyethanol in female BALB/c mice. International Journal of Toxicology, 21: 107-115.

Udden M.M. (2000). Rat erythrocyte morphological changes after gavage dosing with 2-butoxyethanol: a comparison with the *in vitro* effects of butoxyacetic acid on rat and human erythrocytes. Journal of Applied Toxicology, 20: 381-387.

Udden MM (2002). *In vitro* sub-hemolytic effects of butoxyacetic acid on human and rat erythrocytes. Toxicological Sciences, 69: 258-264.

Additional Data on Current Uses of 2-Butoxyethanol in Canada

ToxEcology. 2003. 2-Butoxyethanol and 2-Methoxyethanol. Current Use Patterns in Canada, Toxicology Profiles of Alternatives, and Feasibility of Performing an Exposure Assessment Study. Prepared under contract for Health Canada by ToxEcology – Environmental Consulting Ltd., Vancouver, B.C., Canada.

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or by emailing:

PSL.LSIP@ec.gc.ca

addendum

Unpublished supporting documentation, which presents additional information, is available upon request from:

Exisiting Substances Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

Existing Substances Division
Environmental Health Centre
Health Canada
Tunney's Pasture
Address Locator 0801C2
Ottawa, Ontario
K1A 0L2

103-07080/

Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

2-Butoxyethanol

Environment Canada
Health Canada

August 2002

TABLE OF CONTENTS

SYNOPSIS 1

1.0 INTRODUCTION 3

2.0 SUMMARY OF INFORMATION CRITICAL TO ASSESSMENT OF "TOXIC" UNDER CEPA 1999 7

2.1 **Identity and physical/chemical properties** 7

2.2 **Entry characterization** 7
2.2.1 Production, importation and uses 7
2.2.2 Sources and releases 8
2.2.2.1 Natural sources 8
2.2.2.2 Anthropogenic sources 8

2.3 **Exposure characterization** 8
2.3.1 Environmental fate 8
2.3.1.1 Air 8
2.3.1.2 Water 8
2.3.1.3 Soils 9
2.3.1.4 Biota 9
2.3.1.5 Environmental distribution 9
2.3.2 Environmental concentrations 9
2.3.2.1 Multimedia exposure study 9
2.3.2.2 Ambient air 10
2.3.2.3 Indoor air 10
2.3.2.4 Surface water 11
2.3.2.5 Groundwater 11
2.3.2.6 Drinking water 11
2.3.2.7 Soil 11
2.3.2.8 Food 11
2.3.2.9 Consumer products 11
2.3.2.10 Fugacity modelling 12

2.4 **Effects characterization** 13
2.4.1 Ecotoxicology 13
2.4.1.1 Terrestrial organisms 13
2.4.1.2 Aquatic organisms 13
2.4.2 Abiotic atmospheric effects 13
2.4.3 Experimental animals and in vitro 14
2.4.3.1 Kinetics and metabolism 14
2.4.3.2 Acute toxicity 14

2.4.3.3 Short-term toxicity 15
2.4.3.4 Subchronic toxicity 16
2.4.3.4.1 Oral 16
2.4.3.4.2 Inhalation 16
2.4.3.4.3 Dermal 17
2.4.3.5 Chronic toxicity and carcinogenicity 17
2.4.3.6 Genotoxicity 19
2.4.3.7 Developmental and reproductive toxicity 20
2.4.3.8 Immunotoxicity 20
2.4.3.9 Neurotoxicity 21
2.4.3.10 Investigations of hemolysis in *in vitro* systems 21
2.4.3.11 Toxicokinetics and Mode of Action 22
2.4.4 Humans 23

3.0 ASSESSMENT OF "TOXIC" UNDER CEPA 1999 25

3.1 CEPA 1999 64(a): Environment 25
3.1.1 Assessment endpoints 25
3.1.2 Environmental risk assessment 25
3.1.2.1 Terrestrial organisms 25
3.1.2.1.1 Wildlife 25
3.1.2.1.2 Soil organisms 26
3.1.2.2 Aquatic organisms 26
3.1.2.3 Discussion of uncertainty 27

3.2 CEPA 1999 64(b): Environment upon which life depends 27

3.3 CEPA 1999 64(c): Human health 27
3.3.1 Estimates of potential exposure in humans 27
3.3.2 Human health hazard characterization 32
3.3.2.1 Hematological effects 32
3.3.2.2 Other non-neoplastic effects 33
3.3.2.3 Carcinogenicity and genotoxicity 34
3.3.3 Exposure–response analyses 34
3.3.3.1 Hematological effects 35
3.3.3.2 Other (non-hematological) effects 44
3.3.4 Risk characterization 45
3.3.5 Uncertainties and degree of confidence in the human health risk characterization 47

3.4 Conclusions 49

3.5 Considerations for follow-up (further-action) 50

4.0 REFERENCES 51

APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA 61

List of Tables

Table 1 Effects of concentration and time on hematocrit and the concentration of free plasma hemoglobin in rat blood incubated with butoxyacetic acid (BAA) *in vitro* 22

Table 2 Effects of concentration, time and sex on hematocrit and the concentration of free plasma hemoglobin in human blood incubated with butoxyacetic acid (BAA) *in vitro* 23

Table 3 Estimated average intake of 2-butoxyethanol by six age groups in the general population 28

Table 4 Estimates of exposure to 2-butoxyethanol through inhalation and dermal uptake from use of household cleaning products 30

Table 5 BMC_{05}s and model fitting information for hematological effects in mice 41

Table 6 BMC_{05}s and model fitting information for hematological effects in rats 42

Table 7 BMC_{05}s and model fitting information for other non-hematological endpoints 45

List of Figures

Figure 1 Exposure–response curves for hematological effects in mice and rats 37

Figure 2 Exposure–response curves for non-hematological effects in mice and rats 46

List of Acronyms and Abbreviations

AUC	area under the curve
BAA	2-butoxyacetic acid
BMC	Benchmark Concentration
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CFC	chlorofluorocarbon
CTV	Critical Toxicity Value
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
GWP	Global Warming Potential
HC_5	hazardous concentration to 5% of test species
K_{oc}	organic carbon sorption coefficient
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LCL	lower confidence limit
LD_{50}	median lethal dose
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEL	Lowest-Observed-Effect Level
NOEL	No-Observed-Effect Level
NTP	National Toxicology Program
ODP	Ozone Depletion Potential
PBPK	physiologically based pharmacokinetic
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List
TC	Tolerable Concentration
VOC	volatile organic compound

SYNOPSIS

2-Butoxyethanol is not commercially produced in Canada. It is imported for use mainly as a component of formulations, as part of consumer products or manufactured articles, and as a chemical processing aid. Most reported environmental releases are to the atmosphere, with some minor releases to water.

2-Butoxyethanol reacts with hydroxyl radicals in the air with a half-life of a few hours to about a day. Most of the 2-butoxyethanol released to the atmosphere is predicted to remain in air, with some partitioning to water and soil. 2-Butoxyethanol is biodegraded in water and soil, with an estimated half-life of 1–4 weeks. It has a low octanol/water partition coefficient and is therefore not expected to bioaccumulate to any significant degree. Only limited data are available on concentrations of 2-butoxyethanol in the environment in Canada or elsewhere.

Data on toxicity were identified for aquatic organisms, including microorganisms, invertebrates and fish. The most sensitive species reported, based on acute exposure, is the grass shrimp (*Palaemonetes pugio*).

Because of the limitations of environmental monitoring data, exposures for environmental compartments other than air were estimated based on modelling. Estimated environmental concentrations of 2-butoxyethanol are a few orders of magnitude less than the adverse effects thresholds calculated for sensitive organisms.

2-Butoxyethanol is not involved in stratospheric ozone depletion and is not an important contributor to climate change or ground-level ozone formation.

Based on the limited data identified, inhalation of 2-butoxyethanol in air is an important route of exposure, with estimated exposure through use of consumer products containing the substance being considerable. No data were identified concerning the contribution of food to overall exposure to 2-butoxyethanol.

Based primarily on investigations in experimental animals, the principal critical health effects associated with exposure to 2-butoxyethanol are alterations in hematological parameters associated with hemolysis. Tolerable Concentrations for these effects and for lesions of the forestomach in mice, for which information on mode of action is inadequate to preclude their relevance to humans, were developed, based on Benchmark Concentrations. A Tolerable Concentration is the level of exposure to which it is believed a person may be exposed daily over a lifetime without deleterious effect.

Levels of 2-butoxyethanol in ambient air in Canada are less than the Tolerable Concentrations derived for effects on the blood or forestomach. However, exposure to 2-butoxyethanol during use of products containing the substance could potentially exceed the Tolerable Concentrations, based on limited data on emissions from products currently available in Canada.

Based on available data, it is concluded that 2-butoxyethanol is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity; or constitute or may constitute a danger to the environment on which life depends. 2-Butoxyethanol is considered to be entering the environment in a quantity or concentration or under conditions that constitute or may

constitute a danger in Canada to human life or health. Therefore, 2-butoxyethanol is considered to be "toxic" as defined in Section 64 of CEPA 1999.

Additional characterization of the ranges and distributions of concentrations of 2-butoxyethanol in consumer products currently available in Canada and their emissions is considered a clear priority as a basis for risk management.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" or capable of becoming "toxic" as defined in Section 64 of the Act, which states:

> ...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (b) constitute or may constitute a danger to the environment on which life depends; or
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale for assessing 2-butoxyethanol (along with 2-methoxyethanol and 2-ethoxyethanol) provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> Potential sources of exposure to these compounds include releases from various industrial and consumer uses. These compounds are widely used as solvents in paints and protective coatings; in printing inks, industrial solvents and cleaners; in the production of plasticizers; as a de-icer in fuels and automotive brake fluids; and in electronics manufacturing. Effects due to exposure include disorders of the central nervous system, blood system, kidneys and liver in both humans and animals. An assessment is required to determine the presence of these substances in the Canadian environment, exposure and the potential risks to human health.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*, Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

> Environmental Protection Publications
> Environmental Technology Advancement Directorate
> Environment Canada
> Ottawa, Ontario
> K1A 0H3

An electronic version (PDF file) may be requested from: PSL.LSIP@ec.gc.ca. It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to assessment of effects on human health is outlined in the following publication of the Safe Environments Program (formerly the Environmental Health Directorate) of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Existing Substances Division
Health Canada
Environmental Health Centre
Tunney's Pasture
Address Locator 0801C2
Ottawa, Ontario
K1A 0L2

or on the Safe Environments Program (formerly the Environmental Health Directorate) publications web site (www.hc-sc.gc.ca/hecs-sesc/exsd/psap.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al.*, 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Existing Substances Division web site (www.hc-sc.gc.ca/exsd-dse) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of data relevant to the assessment of entry, environmental fate and exposure, and potential effects on the environment (prior to October 1999) as well as assessment of potential human exposure and health effects (prior to October 1999) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether 2-butoxyethanol is "toxic" under CEPA 1999 have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

Sections of the Assessment Report related to the environmental assessment of 2-butoxyethanol and the environmental Supporting Document (Environment Canada, 1999) were prepared or reviewed by the following members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

D. Boersma, Environment Canada
R. Breton, Environment Canada
P. Cureton, Environment Canada
N. Davidson, Environment Canada
R. Desjardins, Environment Canada
L. Hamel, Union Carbide Canada Inc.
B. Lee, Environment Canada
S. Lewis, American Chemistry Council
B. Sebastien, Environment Canada
K. Taylor, Environment Canada (lead for the environmental assessment)

Sections of the Assessment Report relevant to the environmental assessment and the environmental Supporting Document were also reviewed by C. Staples (Assessment Technologies Inc.).

A summary of data relevant to assessment of the potential risk to human health associated with exposure to 2-butoxyethanol was prepared in 1996 by BIBRA Toxicology International. Additional recent reviews were also used for the identification of relevant data, including those prepared for the International Programme on Chemical Safety (IPCS, 1998) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1998). Additional and more recent data have been identified through searching the on-line databases listed in Appendix A.

Sections of the Assessment Report related to human health and the relevant supporting documentation were prepared by the following staff of Health Canada:

K. Hughes
M.E. Meek
D. Moir
L. Turner
M. Walker

H. Atkins (Ottawa Hospital, General Campus) provided advice on the biological significance of hematological effects. A. Renwick (University of Southampton) provided advice on the adequacy of data as a basis for replacement of default components of uncertainty factors. Input on this aspect was also received at a workshop of the International Programme on Chemical Safety on uncertainty and variability in risk assessment, held in Berlin, Germany, on May 9–11, 2000.

Comments primarily on the adequacy of coverage in the sections of the supporting documentation related to health effects were provided in a written review by members of the American Chemistry Council Ethylene Glycol Ethers Panel, including:

R. Boatman, Eastman Kodak (for Eastman Chemical)
R. Gingell, Shell Chemical
S. Lewis, American Chemistry Council
A. Schumann, Dow Chemical
T. Tyler, Union Carbide Corporation

Comments on accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization were provided in written review by BIBRA International and H. Atkins (Ottawa Hospital, General Campus).

Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and exposure–response analyses were considered in written review of the completed Assessment Report by:

H. Clewell, K.S. Crump Group, Inc., ICF Kaiser International, Inc.
J. Delic, U.K. Health and Safety Executive
J. Gift, National Center for Environmental Assessment, U.S. Environmental Protection Agency
J. Roycoft, National Institute for Environmental Health Sciences

The health-related sections of the Assessment Report were reviewed and approved by the Healthy Environments and Consumer Safety Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

A draft of the Assessment Report was made available for a 60-day public comment period (August 19 to October 18, 2000) (Environment Canada and Health Canada, 2000). Following consideration of comments received, the Assessment Report was revised as appropriate. A summary of the comments and responses is available on the Internet at: www.ec.gc.ca/substances/ese/eng/psap/final/main.cfm. Sections of the revised Assessment Report relevant to human exposure were considered in written review by V.C. Armstrong (consultant), J. Buccini (consultant) and J. Schaum (U.S. Environmental Protection Agency).

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or by emailing:

PSL.LSIP@ec.gc.ca

Unpublished supporting documentation, which presents additional information, is available upon request from:

Exisiting Substances Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

Existing Substances Division
Environmental Health Centre
Health Canada
Tunney's Pasture
Address Locator 0801C2
Ottawa, Ontario
K1A 0L2

2.0 Summary of Information Critical to Assessment of "Toxic" under CEPA 1999

2.1 Identity and physical/chemical properties[1]

2-Butoxyethanol has the empirical molecular formula $C_6H_{14}O_2$, the structural formula $CH_3CH_2CH_2CH_2OCH_2CH_2OH$ and a molecular weight of 118.2. Its Chemical Abstracts Service (CAS) Registry Number is 111-76-2. 2-Butoxyethanol is a colourless liquid with a water solubility of 63 500 mg/L at 25°C, an octanol/water partition coefficient (log K_{ow}) of 0.84, a vapour pressure of 296 Pa at 25°C and a calculated Henry's law constant of 0.551 Pa·m³/mol (ASTER, 1996). The conversion factor for air is 1 ppm = 4.83 mg/m³.

Synonyms for 2-butoxyethanol include 2-butoxy-1-ethanol; ethylene glycol, monobutyl ether; and butyl cellosolve.

2.2 Entry characterization

2.2.1 Production, importation and uses

2-Butoxyethanol was not produced in Canada in 1995 or 1996, according to data reported to Environment Canada from 188 companies through a survey carried out under the authority of Section 16 of the 1988 *Canadian Environmental Protection Act* (CEPA). Importation of 2-butoxyethanol into Canada was 6.0 kilotonnes in 1995 and 6.5 kilotonnes in 1996. Exports of 2-butoxyethanol totalled 35.9 tonnes in 1995 and 34.3 tonnes in 1996 (Environment Canada, 1997b).

2-Butoxyethanol has been used in paints, coatings, inks, cleaners, polishes, brake fluids and jet fuels and has been widely used as a solvent, chemical intermediate and solvent coupler of mixtures and water-based formulations (Stemmler *et al.*, 1997). It is used as a solvent in surface coatings, such as spray lacquers, quick-dry lacquers, enamels, varnishes and latex paint, as well as in varnish removers; as a coupling agent in metal cleaning formulas and household cleaners; and as a component in herbicides and automotive brake fluids (U.S. Department of Health and Human Services, 1990). It has also been used as an ice fog suppressant (U.S. EPA, 1979).

In a CEPA Section 16 survey of 188 companies, it was reported that 5.7 kilotonnes of 2-butoxyethanol were used in Canada in 1995 and 6.1 kilotonnes in 1996, mainly as a component of formulations, as part of consumer products or manufactured articles, or as a chemical processing aid (Environment Canada, 1997b).

2-Butoxyethanol is present in approximately 73 pesticides currently registered for use in Canada, but not in those expected to be used on food commodities. It is used in domestic insecticides, pet sprays, bear/dog deterrents and pesticides used for cleaning/disinfecting purposes and to control aquatic weeds (Health Canada, 1998b).

[1] See the environmental Supporting Document (Environment Canada, 1999) for a more complete listing of ranges of values reported and criteria for selection of physical and chemical properties.

2.2.2 *Sources and releases*

2.2.2.1 Natural sources

No information has been found to indicate that 2-butoxyethanol occurs as a natural product. There are no known reactions that would lead to the *in situ* production of 2-butoxyethanol or other glycol ethers in the atmosphere (Rogozen *et al.*, 1987).

2.2.2.2 Anthropogenic sources

Information about 2-butoxyethanol was not available from the National Pollutant Release Inventory, because the substance was added to the inventory only in 1999.

According to data reported under the CEPA Section 16 survey, 319 tonnes of 2-butoxyethanol were released into the air in Canada in 1996, while 63 tonnes were released as waste, 6.5 tonnes were released into landfills and 2 tonnes were released into water (Environment Canada, 1997b).

The Canadian Chemical Producers' Association (1997) reported total environmental emissions of 2-butoxyethanol of 1.0, 3.0, 2.0 and 1.0 tonne by member companies in 1992, 1993, 1994 and 1995, respectively, all of which were released to air. Reported emissions totalled 1.0 tonne in 1996, 2.0 tonnes in 1997 and 1.0 tonne in 1998 (Canadian Chemical Producers' Association, 1999a,b).

2-Butoxyethanol was detected at a concentration of 0.23 $\mu g/m^3$ in the emissions of a municipal waste incineration plant in Germany (Jay and Stieglitz, 1995).

Leachate from municipal landfills and hazardous waste sites can release 2-butoxyethanol to groundwater (Brown and Donnelly, 1988; Howard, 1993). Concentrations of 2-butoxyethanol in aqueous samples from a municipal and an industrial landfill in the United States ranged from <0.4 to 84 mg/L (Beihoffer and Ferguson, 1994).

2.3 Exposure characterization

2.3.1 *Environmental fate*

2.3.1.1 Air

In air, 2-butoxyethanol is expected to exist almost entirely in the vapour phase, and reactions with photochemically produced hydroxyl radicals should be important. Tuazon *et al.* (1998) reported that the gas-phase reaction products of 2-butoxyethanol with hydroxyl radicals in the presence of nitric oxide were n-butyl formate, 2-hydroxyethyl formate, propanal, 3-hydroxybutyl formate, an organic nitrate and one or more hydroxycarbonyl products. Stemmler *et al.* (1997) irradiated synthetic air mixtures containing 2-butoxyethanol, methyl nitrite and nitric oxide in a Teflon bag reactor at room temperature. Themajor oxidation products were butyl formate, ethylene glycol monoformate, butoxyacetaldehyde, 3-hydroxybutyl formate and propionaldehyde, whereas minor products were 2-propyl-1,3-dioxolane, ethylene glycol monobutyrate, 2-hydroxybutyl formate, acetaldehyde, propyl nitrate and butyraldehyde. Physical removal of 2-butoxyethanol from air by precipitation and dilution in clouds may occur; however, its short atmospheric residence time indicates that wet deposition is of limited importance (Howard, 1993). Howard *et al.* (1991) estimated a half-life of 2-butoxyethanol in air of 3.28–32.8 hours, based on photooxidation.

2.3.1.2 Water

Howard *et al.* (1991) estimated that the unacclimated biodegradation half-life of 2-butoxyethanol in water would be 1–4 weeks under aerobic conditions. Because of its low log K_{ow} and Henry's law constant, adsorption to particulates and volatilization from surface water are not expected to be important fate processes for 2-butoxyethanol (SIDS, 1996).

Because of its low organic carbon sorption coefficient (K_{oc} = 67; Lyman *et al.*,

1990), 2-butoxyethanol should be highly mobile in soil and potentially could reach groundwater if released into soil (SIDS, 1996). Howard *et al.* (1991) estimated a half-life of 2-butoxyethanol in groundwater would be 2–8 weeks, based on unacclimated aqueous aerobic biodegradation.

2.3.1.3 Soils

Howard *et al.* (1991) estimated that the half-life of 2-butoxyethanol in soil would be 1–4 weeks, based on unacclimated aqueous aerobic biodegradation.

2.3.1.4 Biota

A bioconcentration factor of 2.5 was calculated for 2-butoxyethanol (SRC, 1988). Bioaccumulation of 2-butoxyethanol in aquatic organisms would therefore not be significant.

2.3.1.5 Environmental distribution

A Level III fugacity model was used to estimate the environmental partitioning of 2-butoxyethanol when released into air, water or soil. Values for input parameters were as follows: molecular weight, 118 g/mol; vapour pressure, 296 Pa; water solubility, 63 500 mg/L; log K_{ow}, 0.84; Henry's law constant, 0.551 Pa·m³/mol; half-life[2] in air, 17 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. Modelling was based upon an assumed emission rate of 1000 kg per hour, although the emission rate used would not affect the estimated percent distribution. If 2-butoxyethanol were emitted into air, EQC (Equilibrium Criterion) Level III fugacity modelling predicts that about 66% would be present in air, about 20% in water and about 14% in soil. If 2-butoxyethanol were emitted into water, more than 99% would be present in water. If 2-butoxyethanol were released to soil, about 75% would be present in soil and about 25% in water.

2.3.2 Environmental concentrations

Few data on levels of 2-butoxyethanol in the environment have been identified for Canada or elsewhere. One study was conducted to determine concentrations of 2-butoxyethanol in multiple media to which humans are exposed in Canada, including drinking water and indoor and outdoor air (Conor Pacific Environmental Technologies Inc., 1998), as outlined below in Section 2.3.2.1. Additional data on levels of 2-butoxyethanol in specific media are presented in the subsequent sections.

2.3.2.1 Multimedia exposure study

2-Butoxyethanol was among the target volatile organic compounds (VOCs) in the second phase of a Health Canada-sponsored multimedia exposure study, which was conducted during 1997 (Conor Pacific Environmental Technologies Inc., 1998). However, analytical compromises to simultaneously determine low concentrations of numerous, diverse VOCs in various sample types adversely impacted the quality of the data obtained for 2-butoxyethanol. Consequently, confidence in the results of this study is low, due to limitations of the analytical methods involved, as discussed in Section 3.3.5.

Exposure to the target VOCs was measured for 50 participants from three different geographical areas across Canada. Thirty-five participants were randomly selected from the Greater Toronto area in Ontario, six from Queens

[2] For each environmental compartment, DMER and AEL (1996) use a series of ranges of half-life times (<10 hours, 10–30 hours, 30–100 hours, etc.), and the half-life of the particular substance is assigned to the appropriate range, based on a consideration of available persistence data. The geometric mean of this range is then used as an input parameter for the fugacity model. For example, the atmospheric half-life of 2-butoxyethanol in air is judged to be between 10 and 30 hours. The geometric mean of this range, 17 hours, is used as an input parameter in the model. Conservative values for persistence were selected, i.e., longer rather than shorter half-lives, to ensure that persistence was not underestimated.

Subdivision in Nova Scotia and nine from Edmonton, Alberta. For each participant, samples of drinking water, and beverages and indoor, outdoor and personal air were collected over a single 24-hour period. Samples of foods were not analysed for 2-butoxyethanol (Conor Pacific Environmental Technologies Inc., 1998).

The limit of detection for 2-butoxyethanol in samples of air collected for 24-hour periods with passive sampling devices was 0.84 μg/m³. Although confidence in the individual measurements is low due to high and variable blanks and low extraction recovery, the arithmetic mean concentrations[3] of 2-butoxyethanol in outdoor, indoor and personal air samples were 8.4, 27.5 and 31 μg/m³, respectively, with maxima of 243, 438 and 275 μg/m³, respectively. Although confidence in quantitation for individual determinations is low, the quality of data is sufficient to confirm that levels in indoor air are greater than those in ambient air, based on consideration of arithmetic mean concentrations (i.e., 27.5 μg/m³ in indoor air versus 8.4 μg/m³ in outdoor air).

2-Butoxyethanol was detected in 68% of the 50 drinking water samples (detection limit 0.02 μg/L). Concentrations ranged from below the limit of detection to 0.94 μg/L, with a mean concentration of 0.21 μg/L. Duplicate portions of beverages consumed were collected and combined to provide a single composite beverage sample for each study participant. 2-Butoxyethanol was detected in 56% of the 50 beverage samples (detection limit 6.80 μg/L). Concentrations ranged up to 73.8 μg/L, and the mean concentration was 6.46 μg/L. As only composite samples were analysed, no information is available with regard to the type(s) of beverage(s) that contained detectable concentrations of 2-butoxyethanol.

2.3.2.2 Ambient air

In the Windsor Air Quality Study, the concentrations of 2-butoxyethanol in 24 samples of ambient air collected in the vicinity of an automotive plant and in 7 samples collected in downtown Windsor were measured. Concentrations of 2-butoxyethanol were less than the limit of detection (3.3 μg/m³) in all the samples collected in downtown Windsor. Of the 24 samples collected at the automotive plant, concentrations of 2-butoxyethanol were above the limits of detection (which ranged from 0.65 to 1.3 μg/m³) in 16 (67%); the mean value for these samples was 2.3 μg/m³, when concentrations in samples where 2-butoxyethanol was not detected were assumed to be equivalent to one-half the limit of detection, and the maximum concentration was 7.3 μg/m³. The authors stated that the probable source of 2-butoxyethanol in ambient air samples downwind of the plant was from paints and lacquers in which 2-butoxyethanol is used as a solvent (OMEE, 1994).

Similar levels were reported in outdoor air in other countries. In samples of ambient air collected between 1990 and 1993 in countries other than Canada, concentrations of 2-butoxyethanol ranged from below the limits of detection to 21 ppb (101 μg/m³) (Ciccioli *et al.*, 1993, 1996; Daisey *et al.*, 1994; Brinke, 1995; Shields *et al.*, 1996). 2-Butoxyethanol has also been quantified in air from Terra Nova Bay, Antarctica, at concentrations ranging from 1.3 to 15 μg/m³ (Ciccioli *et al.*, 1996).

2.3.2.3 Indoor air

Available data on concentrations of 2-butoxyethanol in residential indoor air, other than those for the multimedia investigation described in Section 2.3.2.1, are limited to detection of 2-butoxyethanol at a concentration of 8 μg/m³ in one of six samples of indoor air collected over 4-to 7-day periods in 1983–1984 from homes in northern Italy (De Bortoli *et al.*, 1986). Concentrations of 2-butoxyethanol in the other five samples were below the limit of detection, which was not specified.

---

[3] In all outdoor air, indoor air, personal air, drinking water and beverage samples where 2-butoxyethanol was not detected, concentrations were assumed to be equivalent to one-half the limit of detection for the calculation of the mean concentration.

2-Butoxyethanol was measured in indoor air samples (three per site) at concentrations up to 33 μg/m³ during March and April 1991 at 70 office buildings in 25 states plus the District of Columbia across the United States (Shields *et al.*, 1996). A specific limit of detection was not reported for 2-butoxyethanol; however, a general limit of detection of 0.5 μg/m³ was reported for VOCs. Geometric mean concentrations calculated based on the assumption of half of this general limit of detection (0.25 μg/m³) for samples in which the concentration of 2-butoxyethanol was below the limit of detection are reported for three categories of building. 2-Butoxyethanol was detected in 24% of the samples from 50 telecommunications offices at concentrations up to 33 μg/m³; the geometric mean concentration was 0.1 μg/m³. The compound was detected in 44% of the samples from nine data centres at concentrations up to 16 μg/m³, with a geometric mean concentration of 0.2 μg/m³. 2-Butoxyethanol was also detected in 73% of the samples from 11 administrative offices at concentrations up to 32 μg/m³, with a geometric mean concentration of 1.0 μg/m³ (Shields *et al.*, 1996). In contrast, detectable concentrations of 2-butoxyethanol were not present in 70 samples of outdoor air collected in the immediate vicinities of these office buildings.

Indoor air was sampled between June and September 1990 in 12 office buildings in the San Francisco Bay area of northern California. Concentrations of 2-butoxyethanol ranged from below the limit of detection (0.4 ppb or 1.9 μg/m³) to 27 ppb (130 μg/m³). An arithmetic mean concentration was not reported. The geometric mean concentration was 1.6 ppb (7.7 μg/m³) in indoor air, compared with 0.39 ppb (1.9 μg/m³) in the air outside these buildings (Daisey *et al.*, 1994; Brinke, 1995). However, the number of samples collected at each location, the frequencies of detection in indoor air and key details of the sampling and analytical methods were not reported.

2.3.2.4 Surface water

Water samples taken from a polluted river in Japan in 1980 contained 2-butoxyethanol at a concentration of 1.31–5.68 mg/L (Yasuhara *et al.*, 1981).

2.3.2.5 Groundwater

No data were identified on the concentration of 2-butoxyethanol in groundwater in Canada or elsewhere.

2.3.2.6 Drinking water

In 29 samples of drinking water collected between 1989 and 1995 from four sites in Ontario, concentrations of 2-butoxyethanol were above the limit of detection (not specified) in one sample from each site (i.e., in 9–17% of total samples at each site). The highest concentration (5.0 μg/L) was measured in a sample collected in Port Dover (OMEE, 1996).

2.3.2.7 Soil

No data were identified on the concentration of 2-butoxyethanol in soil in Canada or elsewhere.

2.3.2.8 Food

Data on the levels of 2-butoxyethanol in food were not identified; however, 2-butoxyethanol was detected but not quantified in a sample of paper and paperboard food packaging materials in the United Kingdom (Castle *et al.*, 1997).

2.3.2.9 Consumer products

2-Butoxyethanol is used as a solvent in a number of consumer products, including paints, paint thinners and cleaning products. In Canada, there are no regulations concerning permissible levels of glycol ethers, including 2-butoxyethanol, in consumer products (Health Canada, 1998a). Material Safety Data Sheets list the percent contents of 2-butoxyethanol as up to 5% in latex paints and up to 30% in paint thinners (General Paint Ltd., 1997). Of the cosmetic products

currently registered for sale in Canada. 2-butoxyethanol is a registered component in 63 products, including hair dyes, manicure preparations (nail polishes and nail polish removers) and skin cleansers. Most of these products were reported to contain 2-butoxyethanol concentrations in the range of 3–10%, with one cleanser containing 1–3% and two nail polishes containing 0.1% or less (Health Canada Cosmetic Notification System, 2001). (The *Food and Drugs Act* stipulates that manufacturers and importers of new cosmetic products are required to notify Health Canada concerning the ingredients.) 2-Butoxyethanol is present in approximately 73 pesticides currently registered for use in Canada (see Section 2.2.1).

Concentrations of 2-butoxyethanol of up to 20% were reported in various cleaning products, including degreasers, polishes and windshield washer fluid, used in the United States (Flick, 1986, 1989). "Low-pollutant" paints contained up to 6% 2-butoxyethanol in a study conducted in Germany (Plehn, 1990). Industrial window cleaners used in France were reported to contain 0.9–21.2% 2-butoxyethanol (Vincent *et al.*, 1993). In Australia, 434 cleaning products were reported to contain 2-butoxyethanol in 1994, at concentrations ranging from <1 to 94% (two-thirds of these contained less than 10%); many of these products were intended for industrial use or use in diluted form (National Industrial Chemicals Notification and Assessment Scheme, 1996).

Emissions of 2-butoxyethanol from 13 consumer products purchased in the Ottawa, Ontario, area were recently investigated by Health Canada (Cao, 1999; Zhu *et al.*, 2001). Products selected were those that were believed most likely to contain 2-butoxyethanol, on the basis of other data presented here. 2-Butoxyethanol was detected in emissions from seven products, including cleaners, nail polish remover and hair colorant, at rates of up to 938 mg/m^3 per hour. Analyses of the products indicated that the cleaners contained 0.5–3.7% 2-butoxyethanol, while the nail polish remover and hair colorant contained 3.8% and 25%, respectively.

2.3.2.10 Fugacity modelling

ChemCAN (v. 0.95) modelling was used to estimate environmental concentrations of 2-butoxyethanol. This model is a Level III fugacity-based regional model developed to estimate the environmental fate of chemicals in Canada (ChemCAN4, 1996). ChemCAN calculates the distribution of chemicals in the environmental media, the rates of transport and transformation processes, and average concentrations in any of 24 regions or ecozones of Canada. According to a survey conducted under the authority of Section 16 of CEPA, the highest reported recent release of 2-butoxyethanol in Canada was 319 tonnes, from facilities in British Columbia, Ontario and Quebec in 1996, (Environment Canada, 1997b). To make a conservative estimate of environmental concentrations of 2-butoxyethanol, it was assumed, for modelling purposes, that all of this was released into southern Ontario. "Ontario – Mixed Wood Plain" was therefore selected as the geographic region for ChemCAN modelling of 2-butoxyethanol. The input rate was 36.4 kg 2-butoxyethanol per hour, all to the atmosphere. Chemical input values were as follows: molecular weight, 118 g/mol; vapour pressure, 296 Pa; water solubility, 63 500 mg/L; log K_{ow}, 0.84; Henry's law constant, 0.551 Pa·m^3/mol; half-life in air, 17 hours; half-life in water, 550 hours; half-life in soil, 550 hours; and half-life in sediment, 1700 hours. For Ontario – Mixed Wood Plain, environmental characteristics were as follows: total surface area, 169 000 km^2; percentage of area covered by water, 43.8%; average air height, 2 km; average water depth, 20 m; average soil depth, 10 cm; residence time in air, 1.71 days; residence time in water, 618 days; and environmental temperature, 7.4°C.

Environmental concentrations of 2-butoxyethanol in southern Ontario predicted by ChemCAN 4 modelling are as follows: 1.623 ng/m^3 in air; 3.02×10^{-4} µg/L in water; 4.28×10^{-1} ng/g dry weight in soil; and 1.64×10^{-2} ng/g dry weight in sediments. The ChemCAN model estimates average concentrations throughout the region; therefore,

actual concentrations in the vicinity of releases could be higher than those estimated by the model. In addition, industrial releases of 2-butoxyethanol were assumed to be the only source within the geographical area modelled. Estimates of emissions of 2-butoxyethanol to the environment from consumer products used in the region modelled were not available for use as inputs to this model.

2.4 Effects characterization

2.4.1 Ecotoxicology

2.4.1.1 Terrestrial organisms

No information on the effects of 2-butoxyethanol on wildlife was identified. Based on the results of inhalation studies presented in Section 2.4.3, the species that were most sensitive to airborne 2-butoxyethanol were rats and mice. In subchronic toxicity tests, alterations in hematological parameters indicative of hemolytic anemia were observed in female rats and mice at the lowest concentration tested, 31 ppm (150 mg/m^3) (NTP, 1998). Hemolytic anemia was also noted in rats exposed to 31.2 ppm (151 mg/m^3) 2-butoxyethanol in a 2-year bioassay (NTP, 1998).

2.4.1.2 Aquatic organisms

Chronic toxicity data have been identified for protozoans, algae and fish. The most sensitive organism was the blue-green alga, *Microcystis aeruginosa*, with an 8-day toxicity threshold of 35 mg/L for inhibition of growth (Bringmann and Kuehn, 1978). Acute toxicity data have been reported for protozoans, invertebrates and fish. The most sensitive organisms were the grass shrimp (*Palaemonetes pugio*), with a 96-hour LC_{50} of 5.4 mg/L (Biospherics Inc., 1981a), and the mummichog (*Fundulus heteroclitus*), with a 96-hour LC_{50} of 6.7 mg/L (Biospherics Inc., 1981b). These values are much lower than reported values for other organisms. The next most sensitive invertebrate was the oyster (species not stated), with a 96-hour LC_{50} of 89 mg/L (U.S. EPA, 1984). The most sensitive fish species was the bluegill (*Lepomis macrochirus*), with a 96-hour LC_{50} of 127 mg/L (CIBA-GEIGY Corp., 1979), although other authors reported much higher values for this species, as presented in Table 11 of Environment Canada (1999).

2.4.2 Abiotic atmospheric effects

Worst-case calculations were made to determine if 2-butoxyethanol has the potential to contribute to depletion of stratospheric ozone, ground-level ozone formation or climate change (Bunce, 1996).

The Ozone Depletion Potential (ODP) is 0, as 2-butoxyethanol is not a halogenated compound.

The Photochemical Ozone Creation Potential (POCP) was estimated to be 70 (relative to the reference compound ethene, which has a POCP of 100), based on the following formula:

$$POCP = (k_{2\text{-butoxyethanol}}/k_{ethene}) \times (M_{ethene}/M_{2\text{-butoxyethanol}}) \times 100$$

where:

- $k_{2\text{-butoxyethanol}}$ is the rate constant for the reaction of 2-butoxyethanol with OH radicals (2.5×10^{-11} cm^3/mol per second),
- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28.1 g/mol), and
- $M_{2\text{-butoxyethanol}}$ is the molecular weight of 2-butoxyethanol (118 g/mol).

The Global Warming Potential (GWP) was calculated to be 3.1×10^{-5} (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$GWP = (t_{2\text{-butoxyethanol}}/t_{CFC\text{-}11}) \times (M_{CFC\text{-}11}/M_{2\text{-butoxyethanol}}) \times (S_{2\text{-butoxyethanol}}/S_{CFC\text{-}11})$$

where:

- $t_{2\text{-butoxyethanol}}$ is the lifetime of 2-butoxyethanol (0.0016 years),
- $t_{CFC\text{-}11}$ is the lifetime of CFC-11 (60 years),
- $M_{CFC\text{-}11}$ is the molecular weight of CFC-11 (137.5 g/mol),
- $M_{2\text{-butoxyethanol}}$ is the molecular weight of 2-butoxyethanol (118 g/mol),
- $S_{2\text{-butoxyethanol}}$ is the infrared absorption strength of 2-butoxyethanol (2389/cm^2 per atmosphere, default), and
- $S_{CFC\text{-}11}$ is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

These figures suggest that 2-butoxyethanol does not contribute to stratospheric ozone depletion, its potential contribution to climate change is negligible, and its potential contribution to ground-level ozone formation is moderate. The magnitude of these effects would depend on the concentrations of 2-butoxyethanol in the atmosphere, which are estimated to be very low in Canada. 2-Butoxyethanol's contribution to ozone formation is therefore considered negligible compared with those of other more abundant smog-forming substances, such as the reference compound, ethene (Bunce, 1996).

2.4.3 *Experimental animals and* in vitro

2.4.3.1 Kinetics and metabolism

2-Butoxyethanol is rapidly absorbed following oral, inhalation and dermal exposure. Once absorbed, it is rapidly and extensively distributed throughout the body and rapidly eliminated principally in the urine as metabolites and exhaled as carbon dioxide (thus, there is little potential for bioaccumulation). It is metabolized in the liver primarily via alcohol and aldehyde dehydrogenases to 2-butoxyacetaldehyde and 2-butoxyacetic acid (BAA, the principal and putatively active metabolite, representing up to 75% of the absorbed dose). BAA may be subsequently detoxified through conjugation (at least with glutamine in humans, but possibly not in rats) or metabolized to carbon dioxide. Comparatively minor pathways of 2-butoxyethanol metabolism result in the formation of other urinary metabolites, including glucuronide and sulphate conjugates (at least in rats) and ethylene glycol.

Although data are limited, the acetate moiety of 2-butoxyethanol (2-butoxyethyl acetate) appears to be rapidly hydrolysed to 2-butoxyethanol via esterases in several tissues in the body (Johanson, 1988). For this reason, data on the toxicity of 2-butoxyethyl acetate have been included in this assessment.

2.4.3.2 Acute toxicity

Based on LD_{50}s and LC_{50}s, 2-butoxyethanol and its acetate are of low to moderate toxicity to experimental animals following acute exposure. Hematological effects, as well as effects on the liver, kidney, lung and spleen, some of which may be secondary to hematotoxicity, have been observed in animals acutely exposed to lower doses or concentrations. For example, alterations in hematological parameters characteristic of hemolytic anemia have been observed in rats administered single oral doses as low as 125 mg/kg-bw, while hemoglobinuria was noted in older rats following gavage administration of 32 mg/kg-bw (Ghanayem *et al.*, 1987). Exposure to airborne concentrations of 62 ppm (299 mg/m^3) for 4 hours resulted in increased osmotic fragility of erythrocytes (Carpenter *et al.*, 1956), whereas dermal exposure to 260 mg/kg-bw for 6 hours induced hemolysis in rats (Bartnik *et al.*, 1987). Ghanayem *et al.* (1992) and Sivarao and Mehendale (1995) demonstrated that younger blood cells were more resilient to 2-butoxyethanol-induced hemolysis than were older cells, as rats that had been bled several days prior to exposure to a single oral dose were less severely affected than non-bled rats.

2-Butoxyethanol and its acetate are considered to be mildly to severely irritating to the skin and eyes, with the severity increasing with duration of exposure (Carpenter and Smyth, 1946; Smyth *et al.*, 1962; Truhaut *et al.*, 1979; Union Carbide, 1980; Jacobs *et al.*, 1989; Kennah

et al., 1989; Rohm and Haas Co., 1989; Jacobs, 1992; Zissu, 1995).

2.4.3.3 Short-term toxicity

Hematological effects appear to be the most sensitive endpoint in experimental animals following short-term exposure to 2-butoxyethanol by inhalation, ingestion or dermal contact, with rats being more sensitive than mice or rabbits. Hematological changes characteristic of hemolysis (including reductions in the red blood cell count, hemoglobin levels and hematocrit values) have been reported by a number of investigators in rats exposed repeatedly to 2-butoxyethanol for 2–65 days (Grant *et al.*, 1985; Krasavage, 1986; NTP, 1989; Dieter *et al.*, 1990; Ghanayem *et al.*, 1992). In most of those studies in which hematological parameters were measured, these changes were observed at all doses administered by gavage or in the drinking water (i.e., ≥100 mg/kg-bw per day); in only one study in rats exposed for only 3 days (which was designed primarily to investigate developmental toxicity) was a No-Observed-Effect Level (NOEL) of 30 mg/kg-bw per day determined (NTP, 1989). In several of these short-term studies in rats, the hematological changes appeared to be reversible after cessation of exposure (Grant *et al.*, 1985; NTP, 1989; Ghanayem *et al.*, 1992), while in other studies it appeared that tolerance or autoprotection developed in rats repeatedly exposed to 2-butoxyethanol, based on the lessening in severity of effects (Ghanayem *et al.*, 1992; Sivarao and Mehendale, 1995). In general, mice appear to be less sensitive to 2-butoxyethanol-induced hematological effects than rats. At oral doses of 500 mg/kg-bw per day or more, the only effect observed on the blood in mice was a reduction in red blood cell count (Nagano *et al.*, 1979, 1984).

Effects on other organs, including the spleen, liver and kidneys, have also been observed in rats exposed to 2-butoxyethanol, although generally only at doses or concentrations greater than those associated with alterations in hematological parameters. For example, in two studies, changes in relative weights were noted in rats administered oral doses of 100 mg/kg-bw per day or more for 3 days (NTP, 1989) or 125 mg/kg-bw per day for 12 days (Ghanayem *et al.*, 1992); however, no effects on organ weights were observed in other short-term studies in rats administered higher doses for longer durations (Dieter *et al.*, 1990; Exon *et al.*, 1991; NTP, 1993). Similarly, increased weights of spleen and kidney were noted in rats exposed to 200 ppm (966 mg/m^3) 2-butoxyethanol via inhalation (Tyl *et al.*, 1984). In mice, decreased relative thymus weights were noted following administration of doses of 370 mg/kg-bw per day or more (NTP, 1993).

In inhalation studies, hematological changes were noted in rats exposed to 2-butoxyethanol for up to about 30 days at concentrations of 86 ppm (415 mg/m^3) or more, but not at 50 ppm (242 mg/m^3) or lower concentrations (Carpenter *et al.*, 1956; Dodd *et al.*, 1983; Tyl *et al.*, 1984). A reversible increase in erythrocyte fragility was observed in mice exposed to 100 ppm (483 mg/m^3) or higher concentrations, with transient hemoglobinuria being observed at 200 ppm (966 mg/m^3) or more (Carpenter *et al.*, 1956). Indications of hemoglobinuria were also observed in rabbits exposed to 200 ppm (966 mg/m^3) 2-butoxyethanol or 400 ppm 2-butoxyethyl acetate (2616 mg/m^3, equivalent to 1932 mg 2-butoxyethanol/m^3) (Truhaut *et al.*, 1979; Tyl *et al.*, 1984). Alterations in blood parameters were also noted in limited earlier investigations in dogs and monkeys exposed via inhalation, but not in guinea pigs (Carpenter *et al.*, 1956). Non-hematological effects observed in inhalation studies included an increase in weights of spleen and kidney in rats exposed to 200 ppm (966 mg/m^3) 2-butoxyethanol (Tyl *et al.*, 1984) and histopathological changes in the kidney in rabbits exposed to 400 ppm 2-butoxyethyl acetate (2616 mg/m^3, equivalent to 1932 mg 2-butoxyethanol/m^3) (Truhaut *et al.*, 1979).

Alterations in blood parameters were also observed in an earlier investigation in rabbits repeatedly administered 180 mg

2-butoxyethanol/kg-bw per day or more by dermal contact (Union Carbide, 1980).

2.4.3.4 Subchronic toxicity[4]

2.4.3.4.1 Oral

In the only subchronic oral study in rats identified (NTP, 1993), regenerative hemolytic anemia, characterized by decreases in red blood cell count, hemoglobin concentration and hematocrit and increases in mean cell volume, mean cell hemoglobin and reticulocyte count, was observed following exposure to 2-butoxyethanol in the drinking water for 13 weeks. Female F344/N rats were more sensitive than males to 2-butoxyethanol-induced hematological effects, as alterations in most of these parameters were observed in all dose groups (i.e., ≥750 mg/L in drinking water, or ≥82 mg/kg-bw per day) in females and only in the higher dose groups (i.e., ≥1500 mg/L or ≥129 mg/kg-bw per day) in males. Relative weights of several organs were increased, with females again being more sensitive than males. Histopathological changes were observed in the liver, spleen, bone marrow and uterus, with effects (cytoplasmic alteration, possibly associated with enzyme induction) being observed in the liver at all doses in both sexes. The Lowest-Observed-Effect-Level (LOEL) for hematological and hepatic effects was considered to be 750 mg/L, or 69 and 82 mg/kg-bw per day in males and females, respectively.

Hematological parameters were not examined in the two identified subchronic oral studies in mice (Heindel *et al.*, 1990; NTP, 1993). The most sensitive effect observed in $B6C3F_1$ mice administered 2-butoxyethanol in the drinking water for 13 weeks was increased relative kidney weight in female mice at all exposure levels (i.e., ≥750 mg/L or ≥185 mg/kg-bw per day); there were no accompanying histopathological changes in the kidney (NTP, 1993). Altered organ weights (kidney and liver), along with decreased body weights, were also observed in CD-1 mice exposed to a concentration of 2-butoxyethanol in drinking water equivalent to a dose of 1300 mg/kg-bw per day for 15 weeks, although no histopathological changes were noted. These effects were not noted at the lower dose of 700 mg/kg-bw per day (Heindel *et al.*, 1990).

2.4.3.4.2 Inhalation

Based on results of a subchronic inhalation study in F344/N rats exposed to up to 500 ppm (2415 mg/m^3) for 14 weeks (NTP, 1998), there were changes in hematological parameters characteristic of macrocytic, normochromic, responsive anemia (i.e., increased mean cell volume, lack of change in mean cell hemoglobin values and increased reticulocyte count). Females were more sensitive than males, with alterations in hematological parameters observed at the lowest concentration tested (i.e., LOEL of 31 ppm [150 mg/m^3]) in females, while the LOEL in males for these effects was 125 ppm (604 mg/m^3); the NOEL in males was considered to be 62.5 ppm (302 mg/m^3). The severity of these effects increased with concentration in both sexes, and there was no evidence of amelioration in response over time. In addition, in female rats at the higher concentrations, there was an increased incidence of thrombosis in the blood vessels of several tissues as well as bone infarction, which was hypothesized to have resulted from severe acute hemolysis or anoxic damage to endothelial cells, causing compromised blood flow. Other effects consistent with regenerative anemia observed in both male and female rats included excessive hematopoietic cell proliferation in the spleen, hemosiderin pigmentation in the hepatic Kupffer cells and renal cortical tubules and bone marrow hyperplasia. Inflammation and/or hyperplasia of the forestomach also occurred in rats of both sexes exposed to the higher concentrations (250 and 500 ppm [1208 and 2415 mg/m^3]), while changes in relative kidney

[4] In this section, effect levels are presented as LOELs or NOELs; for discussion of the biological significance of the observed effects, see Section 3.3.3.1.

and liver weights were noted at 62.5 ppm (302 mg/m^3) and above in females and 250 ppm (1208 mg/m^3) and above in males.

Hematological effects, consisting of slight changes in red blood cell count, hemoglobin levels and mean corpuscular hemoglobin, were also observed in female Fischer 344 rats exposed to 77 ppm (372 mg/m^3) for 6 weeks (Dodd *et al.*, 1983); however, after 13 weeks of exposure, values for these parameters were generally similar to those of controls (contrary to the observations in this strain of rats by the NTP [1998]). Males appeared to be much less sensitive, as the only effect on blood was a very slight decrease in red blood cell count after 13 weeks at 77 ppm (372 mg/m^3). No indication of hematotoxicity was observed at 25 ppm (121 mg/m^3), which is considered to be the NOEL. No histopathological changes or alterations in clinical chemistry were noted in exposed rats (Dodd *et al.*, 1983). Conversely, however, renal tubular nephritis was reported in Wistar rats (primarily in males) exposed to 100 ppm 2-butoxyethyl acetate (654 mg/m^3, equivalent to 483 mg 2-butoxyethanol/m^3) for 10 months, although there were no hematological effects (based on a limited range of parameters) (Truhaut *et al.*, 1979).

Alterations in hematological parameters indicative of hemolytic anemia (hemoglobin, hematocrit and erythrocyte counts) were also the most sensitive endpoints observed in B6C3F$_1$ mice exposed for 13 weeks (NTP, 1998). However, the anemia in mice was considered to be normocytic, normochromic and responsive (compared to the macrocytic anemia noted in rats), as 2-butoxyethanol did not induce any changes in mean cell volume. In addition, based on the magnitude of the changes, the anemia was less severe in mice than in rats, although females were again more sensitive than males (LOELs in females and males of 31 ppm [150 mg/m^3] and 125 ppm [604 mg/m^3], respectively). As in rats, effects consistent with regenerative anemia (hemosiderin pigmentation and increased hematopoiesis in the spleen) were also observed. The incidence of hyperplasia of the forestomach was increased in female mice exposed to 125 ppm (604 mg/m^3) or more and in males at the highest concentration, 500 ppm (2415 mg/m^3); various lesions also appeared in other tissues in females at 500 ppm (2415 mg/m^3) (a concentration that was also associated with increased mortality in both sexes).

Increased osmotic fragility of erythrocytes, transient hemoglobinuria and reversible changes in liver weights were observed in C3H mice following exposure to concentrations of 2-butoxyethanol of 100 ppm (483 mg/m^3) or more for up to 90 days; however, erythrocytes returned to normal between exposure episodes (Carpenter *et al.*, 1956).

Similar to the results reported for rats in the same study, renal tubular nephritis was observed in rabbits exposed to 100 ppm 2-butoxyethyl acetate (654 mg/m^3, equivalent to 483 mg 2-butoxyethanol/m^3) for 10 months, although there were no effects on hematological or urinalysis parameters (Truhaut *et al.*, 1979).

2.4.3.4.3 Dermal

No overt signs of toxicity and no effects on the weight or microscopic appearance of unspecified organs or on hematology (including osmotic fragility tests) were observed in rabbits administered daily dermal applications (covered) of up to 150 mg 2-butoxyethanol/kg-bw per day for 13 weeks (CMA, 1983).

2.4.3.5 Chronic toxicity and carcinogenicity[5]

Results are available for bioassays in rats and mice exposed to 2-butoxyethanol for 6 hours per day, 5 days per week, for up to 2 years (NTP, 1998). Similar to the critical endpoints observed

[5] In this section, effect levels are presented as LOELs or NOELs; for discussion of the biological significance of the observed effects, see Section 3.3.3.1.

in shorter-term studies, chronic exposure to 31.2 ppm (151 mg/m^3, the lowest concentration tested) 2-butoxyethanol or greater resulted in hemolytic anemia (characterized as macrocytic, normochromic anemia based on decreases in hematocrit, hemoglobin concentrations and erythrocyte counts, increases in mean cell volume and mean cell hemoglobin, and the lack of effect on mean cell hemoglobin concentration) in F344/N rats. Consistent with results observed in earlier studies and toxicokinetic data that indicate slower clearance of the active metabolite, BAA, and greater activity of the relevant isoenzyme in females (see Section 2.4.3.11), in general, the severity of hematological effects was greater in females than in males, with alterations in multiple parameters being observed at the lowest concentration tested (i.e., 31.2 ppm [151 mg/m^3], considered to be the LOEL), while only mean cell volume was affected in males at this concentration. The severity of these effects increased with exposure level and the effects were persistent throughout the 12 months during which hematological parameters were monitored; there was no indication of amelioration over time in males, while in females, there were slight decreases in the magnitude of the changes in some parameters at 12 months. The anemia was considered to be responsive, based on the observation of increased reticulocyte and nucleated erythrocyte counts and a decrease in the myeloid to erythroid ratios.

There was a marginal increase in the incidence of pheochromocytomas (primarily benign, with one case of malignant tumour) of the adrenal gland in female rats at the highest concentration (125 ppm [604 mg/m^3]), which, while not significantly elevated compared with concurrent controls, was greater than the incidence of this lesion observed in historical controls at the National Toxicology Program (NTP). There was also a non-statistically significant increase in the incidence of hyperplasia of the adrenal medulla of females at 125 ppm (604 mg/m^3). No such increases were observed in males. Other exposure-related histopathological changes observed in rats included increased incidences of minimal hyaline degeneration of the olfactory epithelium (which was considered to be adaptive/protective rather than adverse), increased incidences of Kupffer cell pigmentation in the liver of both sexes at the two highest concentrations, and an increase in splenic fibrosis in males at 62.5 ppm (302 mg/m^3) and above. Based on the results of this study, the NTP concluded that there was no evidence of carcinogenic activity in male F344/N rats and equivocal evidence of carcinogenic activity in female rats of this strain, since the slight increase in pheochromocytomas could not be attributed with certainty to exposure to 2-butoxyethanol.

Consistent with the results reported for shorter-term studies, B6C3F$_1$ mice were less sensitive than rats to the hematological effects associated with exposure to 2-butoxyethanol. Anemia, characterized by decreases in hematocrit, hemoglobin concentrations and erythrocyte count, was present in mice exposed to the two higher concentrations (125 and 250 ppm [604 and 1208 mg/m^3]), and there was some evidence of anemia in females at 62.5 ppm (302 mg/m^3), but only at one time point. In general, based on the lack of consistent changes in mean cell volume and mean cell hemoglobin concentrations, the effects were consistent with normocytic, normochromic anemia. Although considered responsive, based on the increased reticulocyte counts, this response ameliorated over time. In addition, contrary to the observations in rats, there were no decreases in myeloid to erythroid ratios; in fact, there were increases in some exposed groups. Thrombocytosis was present in both sexes of mice at all concentrations, based on the increase in platelet counts, with time of appearance being inversely related to concentration. As in rats, females were more sensitive than males, with significant alterations in hematological parameters generally occurring earlier and at lower exposure levels in female mice.

Although mice were less sensitive than rats to the hematotoxicity of 2-butoxyethanol, several other non-neoplastic and neoplastic effects occurred at lower concentrations in mice than

in rats following chronic exposure. There were increased incidences of papillomas or carcinomas (combined) of the forestomach in both sexes, which were statistically significant in females exposed to 250 ppm (1208 mg/m^3) compared with concurrent and historical controls and in males at 125 and 250 ppm (604 and 1208 mg/m^3) compared with historical controls (but not study controls). In addition, the incidence of hyperplasia of the epithelium of the forestomach was significantly increased in a concentration-related manner in all exposed groups, which was accompanied by a concentration-related trend in the incidence of ulcers of the forestomach in female mice. The severity of the epithelial hyperplasia in females also increased with exposure level, as mean severity scores in animals with lesions were 1.8, 2.0, 2.4 and 2.9 at 0, 62.5, 125 and 250 ppm (0, 302, 604 and 1208 mg/m^3), respectively.

There was also a concentration-related increase in the incidence of hemangiosarcomas of the liver in male mice (significant at 250 ppm [1208 mg/m^3]); hemangiosarcomas were also detected in the bone marrow of two mice exposed to 250 ppm (1208 mg/m^3) (one of which also had a hemangiosarcoma in the spleen, while the other had a hemangiosarcoma in the heart) and in one mouse exposed to 62.5 ppm (302 mg/m^3). A significant increase in the incidence of hepatocellular carcinomas was also observed in males at the highest concentration, although the incidence was within the range observed in historical controls. In addition, the incidences of hepatocellular adenomas were lower in exposed mice than in controls, and there was no indication of an association between exposure and induction of a related preneoplastic lesion. In spite of these facts, a potential role of 2-butoxyethanol in the development of malignant liver tumours could not be ruled out, and it was concluded that they may be exposure-related. Hemosiderin pigmentation of the Kupffer cells of minimal severity was also noted in the liver of exposed mice, which did not appear to be directly correlated to the incidence of neoplastic lesions in this organ.

Based on the increased incidence of hemangiosarcoma of the liver (males) and squamous cell papillomas or carcinomas of the forestomach (females), it was concluded that there was some evidence of carcinogenic activity of 2-butoxyethanol in male and female B6C3F$_1$ mice, and the Lowest-Observed-Adverse-Effect Level (LOAEL) for non-neoplastic effects (hematotoxicity and forestomach lesions) was 62.5 ppm (302 mg/m^3) in both sexes.

2.4.3.6 Genotoxicity

The results of available *in vitro* genotoxicity assays in mammalian cell lines have been somewhat mixed. Overall, there is equivocal evidence that 2-butoxyethanol may be very weakly genotoxic *in vitro*, as it was mutagenic at the *hprt* locus in Chinese hamster lung cells (Elias *et al.*, 1996), but not at the *hprt* or *gpt* locus in Chinese hamster ovary cells (Union Carbide, 1989; Chiewchanwit and Au, 1995), and weakly positive or equivocal results were obtained for unscheduled DNA synthesis, micronuclei and mitotic division aberrations/aneuploidy (Union Carbide, 1989; Elias *et al.*, 1996). Results for chromosomal aberrations were negative, while those for sister chromatid exchange were mixed (Union Carbide, 1989; Villalobos-Pietrini *et al.*, 1989; NTP, 1993, 1998; Elias *et al.*, 1996). 2-Butoxyethanol induced cell transformation at high concentrations and also inhibited intercellular communication (Welsch and Stedman, 1984; Kerckaert *et al.*, 1996). However, it is important to note in interpretation of these data that exogenous metabolic activation was incorporated in few of these studies, particularly since the metabolites of 2-butoxyethanol, butoxyacetaldehyde and BAA, were genotoxic in mammalian cells *in vitro* (Elias *et al.*, 1996), with the intermediate butoxyacetaldehyde being significantly more active than the principal metabolite, BAA. Neither 2-butoxyethanol nor its metabolites induced mutations in prokaryotes (Kvelland, 1988; Zeiger *et al.*, 1992; NTP, 1993, 1998; Hoflack *et al.*, 1995; Gollapudi *et al.*, 1996).

In the few *in vivo* studies identified, 2-butoxyethanol did not induce micronuclei in the bone marrow of mice or rats administered up to 1000 mg/kg-bw via intraperitoneal injection (Elias *et al.*, 1996; NTP, 1998) (which is significant in that the hematopoietic system has been demonstrated to be a target of 2-butoxyethanol-induced effects at much lower doses via ingestion and inhalation, some of which might be secondary to toxicity to circulating blood cells), nor were DNA adducts observed in several tissues examined in rats or transgenic mice exposed to 120 mg/kg-bw as a single oral dose or via repeated subcutaneous administration (Keith *et al.*, 1996). Available *in vivo* data for the metabolites are limited to a single study in which BAA also did not induce micronuclei in the bone marrow of mice (Elias *et al.*, 1996).

2.4.3.7 Developmental and reproductive toxicity

In the available studies involving oral, inhalation or dermal exposure of Fischer 344 or Sprague-Dawley rats, CD-1 mice or New Zealand white rabbits, embryotoxic or fetotoxic effects or malformations have generally been observed only at or above doses that were also maternally toxic (Hardin *et al.*, 1984; Schuler *et al.*, 1984; Wier *et al.*, 1987; NTP, 1989; Heindel *et al.*, 1990). Hematological effects were reported in the fetuses of Fischer 344 rats exposed to 300 mg/kg-bw per day (which was also hematotoxic in the dams) (NTP, 1989), suggesting that the blood is also a sensitive target tissue in the developing young following *in utero* exposure. Although a slight decrease in live pup weight was reported in CD-1 mice exposed to 700 mg/kg-bw per day in the drinking water, no statistically significant effects on pup weight were observed in the second generation exposed to the same dose (Heindel *et al.*, 1990).

In the only study on the effects of exposure to 2-butoxyethanol on reproductive ability, fertility in female CD-1 mice (based on litter size and the proportion of live pups) was significantly reduced following administration of 1% 2-butoxyethanol or more in the drinking water (1300 mg/kg-bw per day), although these doses were also associated with high mortality (Heindel *et al.*, 1990). (It has been hypothesized that fetal deaths may have been due to hydrops foetalis, associated with severe anemia induced by 2-butoxyethanol or its metabolite, BAA, transported across the placenta [Atkins, 1999]; however, no description of the possible cause of fetal death was presented in the report of this study.) Effects on male and female reproductive organs (including reduced weight or histopathological changes in the epididymis or testes, decreased sperm concentration, altered sperm morphology or uterine atrophy) were noted in F344 rats and B6C3F$_1$ mice exposed to 2-butoxyethanol in the subchronic studies conducted by the NTP (1993, 1998), although some of these effects were not considered to be of biological significance and occurred only at doses or concentrations that also induced hematological and other effects. No effects on the testes were observed in acute or short-term studies (Nagano *et al.*, 1979, 1984; Doe, 1984; Grant *et al.*, 1985; Krasavage, 1986; Exon *et al.*, 1991).

2.4.3.8 Immunotoxicity

Based on the limited available data, 2-butoxyethanol appears to have some immunomodulating potential, with mice being more sensitive than rats. Significant effects on indicators of immune function were observed in BALB/c mice administered repeated oral doses of 50 mg/kg-bw per day or more (Morris *et al.*, 1996), while only slight or no changes in immune function parameters were noted in Fischer 344 and Sprague-Dawley rats administered higher doses (Exon *et al.*, 1991; Smialowicz *et al.*, 1992). Repeated dermal application of 1500 mg 2-butoxyethanol/kg-bw per day also resulted in reduced immune response in BALB/c mice (Singh *et al.*, 1998); no similar studies in rats were identified. Reduced weights or histopathological changes were observed in the thymus or spleen of both mice and rats exposed subchronically or chronically to 2-butoxyethanol; however, these effects were considered likely to

be secondary to hemolysis and decreased body weight (NTP, 1993, 1998).

2.4.3.9 Neurotoxicity

No investigations of the neurological effects of 2-butoxyethanol have been identified, although various signs of effects on the central nervous system, including loss of coordination, sluggishness, narcosis, muscular flaccidity and ataxia, have been reported at high doses or concentrations in numerous short-term studies (Carpenter *et al.*, 1956; Dodd *et al.*, 1983; Hardin *et al.*, 1984; Krasavage, 1986).

2.4.3.10 Investigations of hemolysis in *in vitro* systems

Differences in species sensitivity to hemolysis induced by 2-butoxyethanol and its metabolites have been investigated in several *in vitro* studies. Consistent with the *in vivo* studies discussed above, BAA was more potent than either the parent compound or the acetaldehyde metabolite (Bartnik *et al.*, 1987; Ghanayem, 1989; Sivarao and Mehendale, 1995). Although slight species differences were observed in erythrocytes exposed to 2-butoxyethanol (with humans being less sensitive than rats, mice, dogs and guinea pigs) (Carpenter *et al.*, 1956; Bartnik *et al.*, 1987), variability between species was much more pronounced when cells were exposed to BAA (Bartnik *et al.*, 1987; Ghanayem and Sullivan, 1993; Udden and Patton, 1994), with erythrocytes from humans being less sensitive than those from rats, as well as those from mice and other species.

In Bartnik *et al.* (1987), hemolysis in blood from four adult male Wistar rats and human erythrocytes isolated from the blood of healthy adult male donors (no further details provided) was examined *in vitro*. The lowest concentration of BAA administered (1.25 mM) resulted in 25% hemolysis of rat erythrocytes after 180 minutes. In contrast, 15 mM BAA did not produce measurable hemolysis in human erythrocytes over the same time. In consequence, these data suggest that rat erythrocytes are at least 12 times more sensitive than the human erythrocytes. This study was conducted in washed erythrocytes rather than whole blood, indicating that the species difference in sensitivity *in vitro* must be due to an inherent difference in the erythrocytes, rather than in the extent of plasma protein binding of BAA.

In Ghanayem (1989), pooled erythrocytes from 9- to 13-week-old male F344 rats and erythrocytes from healthy human volunteers (men and women 18–40 years old; n = 3) were similarly exposed to the acetic acid metabolite. At the end of the incubation period (0.25–4 hours), hematocrit and free plasma hemoglobin levels were determined as indicators of swelling of the erythrocytes and hemolysis, respectively. Comparison of the *in vitro* incubation data at 4 hours for rat blood (Table 1) and human blood (Table 2) suggests that the effect of 8.0 mM BAA in humans was less than that of 0.5 mM BAA in rats. Hence, humans may be at least 16 times less sensitive to the effects of BAA than rats, although information from this study is inadequate to define the exact magnitude of the species difference. It is also not clear from the data presented whether the slight changes with human erythrocytes were produced in relation to the initial control value or were compared with data for a 4-hour incubation in the absence of BAA.

Udden (1994) confirmed the lack of hemolysis in human red blood cells incubated with 2 mM BAA in groups of different human subjects, including nine healthy young adults (31–56 years old), nine older subjects (64–79 years old), seven patients with sickle cell disease and three patients with spherocytosis. Despite differences between these groups in the extent of the spontaneous hemolysis on incubation for 4 hours in the absence of BAA, in none of the groups were there significant increases in hemolysis in the presence of 2 mM BAA.

An additional investigation of Udden and Patton (1994) confirms the greater sensitivity of rat erythrocytes compared with human erythrocytes to the acetic acid metabolite of 2-butoxyethanol *in vitro*. The maximum

TABLE 1 Effects of concentration and time on hematocrit and the concentration of free plasma hemoglobin in rat blood incubated with butoxyacetic acid (BAA) *in vitro* (data from Ghanayem, 1989)

	Time since exposure (hours)				
	0.25	**0.5**	**1.0**	**2.0**	**4.0**
Hematocrit (% control)					
0.5 mM BAA		104	108	110	121
1.0 mM BAA		111	117	124	144
2.0 mM BAA	111	118	133	169	<10
Plasma hemoglobin (g/dL)					
0.5 mM BAA		0.2	0.2	0.2	0.5
1.0 mM BAA		0.4	0.8	1.0	2.0
2.0 mM BAA		0.6	1.0	2.2	7.0

concentration (2 mM) did not produce any detectable effect in human erythrocytes, although it induced rapid hemolysis in rat erythrocytes. Exposure of rat erythrocytes to 0.2 mM BAA did not result in hemolysis, although reduced cell deformability and increased mean cell volume were noted. No details were given of the human subjects who donated erythrocytes.

Comparison of the data of Udden (1994) with those of Udden and Patton (1994), acquired by directly comparable protocols, indicates that the no-effect concentration for hemolysis is 2 mM BAA in human erythrocytes and 0.2 mM in rat erythrocytes. Although very few concentrations were studied, these data support at least a 10-fold difference in sensitivity between rats and humans.

2.4.3.11 Toxicokinetics and mode of action

These observed species- and sex-related variations in hematotoxicity are well correlated with differences in production and clearance of the acetic acid metabolite of 2-butoxyethanol. Mice appear to clear BAA from the blood much more quickly than rats, with the rate of elimination decreasing with increased duration of exposure to a greater degree in rats than in mice (Dill *et al.*, 1998). Likewise, clearance of BAA from the blood is slower in female rats than in males (Dill *et al.*, 1998); in addition, the activity of hepatic alcohol dehydrogenase enzyme, which is involved in the metabolism of 2-butoxyethanol to BAA, is greater in females than in males (Aasmoe *et al.*, 1998). Ghanayem *et al.* (1987) also observed older rats to be more susceptible to the hemolytic effects of acute 2-butoxyethanol exposure, which is consistent with the greater rate of elimination of metabolites in the urine of younger rats. These observations and additional studies in which oxidation of 2-butoxyethanol to BAA is inhibited indicate that the acid metabolite is likely principally responsible for the hematological effects observed in experimental animals exposed to the compound.

The specific mode of action by which 2-butoxyethanol induces hematological effects has not been established. Induced changes are those consistent with hemolytic anemia, hemoglobinuria or increased osmotic fragility of erythrocytes. Based on their progression, which includes erythrocyte swelling, morphological changes and decreased deformability (Udden, 1996), effects are likely due to conjugation of BAA with the lipids in the membrane of erythrocytes and resulting increases in permeability to cations and water (Ghanayem, 1996).

Information on the mode of induction of lesions of the forestomach by 2-butoxyethanol in subchronic studies in rats and mice and in the

TABLE 2 Effects of concentration, time and sex on hematocrit and the concentration of free plasma hemoglobin in human blood incubated with butoxyacetic acid (BAA) *in vitro* (data from Ghanayem, 1989)

	Time since exposure (hours)					
	Males			Females		
	1.0	2.0	4.0	1.0	2.0	4.0
Hematocrit (% control)						
2.0 mM BAA	100.8	102.5	103.2	98.6	100.0	100.2
4.0 mM BAA	102.0	103.0	104.8	100.2	100.8	103.0
8.0 mM BAA	104.0	105.1	108.2	103.6	104.0	106.4
Plasma hemoglobin (g/dL)						
2.0 mM BAA	0.12	0.13	0.20	0.14	0.15	0.17
4.0 mM BAA	0.17	0.22	0.30	0.20	0.25	0.25
8.0 mM BAA	0.40	0.42	0.53	0.35	0.39	0.44

chronic study in mice has not been identified. The relative roles of systemic versus local delivery (i.e., mucociliary clearance from the respiratory tract and ingestion via preening) and the putatively active metabolites, which may differ from those implicated in the induction of hematological effects, are unknown. Specific quantitative data with which to assess the relative sensitivities of the forestomach of rodents and the glandular stomach of humans to 2-butoxyethanol were also not identified.

2.4.4 Humans

Alterations in various hematological parameters were noted in several case reports involving incidental exposure to 2-butoxyethanol (Rambourg-Schepens *et al.*, 1988; Gijsenbergh *et al.*, 1989; Bauer *et al.*, 1992), but not in a survey of childhood poisonings by oral doses estimated to be as high as 1850 mg/kg-bw (Dean and Krenzelok, 1992). In a recent cross-sectional survey, slight, but statistically significant, changes in some hematological parameters (hematocrit and mean corpuscular hemoglobin concentration) were observed in a group of 31 men occupationally exposed to average concentrations of 2-butoxyethanol of 3.64 or 2.20 mg/m^3 compared with unexposed workers, although there was no correlation with levels of butoxyacetic acid in the urine, and information on exposure was limited to personal monitoring samples taken during only one workshift (Haufroid *et al.*, 1997). However, in the only relevant clinical study identified, no changes in erythrocyte fragility were noted in a small number of men and women (n = 2–4) exposed to up to 195 ppm (942 mg/m^3) for several hours, with observed effects limited to irritation of the eyes, nose and throat (Carpenter *et al.*, 1956).

Other effects characteristic of poisoning with ethylene glycol (a metabolite of 2-butoxyethanol in humans), such as coma, metabolic acidosis and renal effects, as well as changes in levels of hepatic enzymes (of uncertain biological significance) have been reported in several cases or cross-sectional studies (e.g., Rambourg-Schepens *et al.*, 1988; Collinot *et al.*, 1996; Haufroid *et al.*, 1997; Nisse *et al.*, 1998).

3.0 ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A conservative (or hyperconservative) quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

In Canada, most environmental releases of 2-butoxyethanol are to the atmosphere. Based on its predicted environmental partitioning, assessment endpoints for 2-butoxyethanol relate to terrestrial biota, pelagic organisms and soil organisms.

3.1.2 Environmental risk assessment

3.1.2.1 Terrestrial organisms

3.1.2.1.1 Wildlife

For a conservative risk characterization for terrestrial biota, the EEV is 243 µg/m^3, the highest concentration of 2-butoxyethanol in outdoor air reported in a Canadian multimedia study. This value is believed to be conservative, because the highest concentration of 2-butoxyethanol in the atmosphere in the vicinity of an automotive plant at Windsor, Ontario, was 7.3 µg/m^3. The estimated concentration of 2-butoxyethanol in Canadian air using ChemCAN modelling based on reported releases in 1996 is several orders of magnitude smaller, 1.623 ng/m^3. Releases of 2-butoxyethanol occurred in three provinces, but, for modelling purposes, it was assumed that all releases occurred in southern Ontario.

The CTV is 31 ppm (150 mg/m^3), the concentration in air that caused hemolytic anemia in rats and mice. Dividing this CTV by a factor of 10 (to account for the extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity) gives an ENEV of 3.1 ppm (15 mg/m^3, or 15 000 µg/m^3).

The conservative quotient can be derived as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{243\ \mu g/m^3}{15\ 000\ \mu g/m^3}$$

$$= 1.6 \times 10^{-2}$$

Therefore, concentrations of 2-butoxyethanol in air appear to be unlikely to cause adverse effects on populations of terrestrial biota.

3.1.2.1.2 Soil organisms

For a conservative risk characterization for soil organisms, the EEV is 4.28×10^{3} ng/g, the estimated concentration of 2-butoxyethanol in soil using ChemCAN modelling, based on reported releases in 1996. This value is believed to be conservative, because releases of 2-butoxyethanol occurred in three provinces, but, for modelling purposes, it was assumed that all releases occurred in southern Ontario.

No information was identified regarding the toxicity of 2-butoxyethanol to soil organisms. Van Leeuwen *et al.* (1992) used quantitative structure–activity relationships to estimate that a sediment concentration of 4600 ng 2-butoxyethanol/g would be hazardous to 5% of benthic species. Using this sediment HC_5 value as a CTV and an application factor of 100 (to account for interspecies and intraspecies variations in sensitivity) gives an ENEV of 46 ng/g for soil organisms.

The conservative quotient is calculated as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{4.28 \times 10^{3} \text{ ng/g}}{46 \text{ ng/g}}$$

$$= 9.3 \times 10^{1}$$

Therefore, concentrations of 2-butoxyethanol in soil in Canada are unlikely to cause adverse effects on populations of soil organisms.

3.1.2.2 Aquatic organisms

For a conservative risk characterization for pelagic organisms, the EEV is 3.02×10^{-4} µg/L, the estimated concentration of 2-butoxyethanol in water using ChemCAN modelling, based on reported releases in 1996. This value is believed to be conservative, because releases of 2-butoxyethanol occurred in three provinces, but, for modelling purposes, it was assumed that all releases occurred in southern Ontario.

The CTV for pelagic organisms is 5.4×10^{3} µg/L, the 96-hour LC_{50} for *Palaemonetes pugio*. Dividing this CTV by a factor of 100 (to account for the conversion of an acute LC_{50} to a long-term no-effects value, extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity) gives an ENEV of 54 µg/L.

The conservative quotient can be derived as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{3.02 \times 10^{-4} \text{ µg/L}}{54 \text{ µg/L}}$$

$$= 5.6 \times 10^{-6}$$

Therefore, 2-butoxyethanol concentrations in water in Canada appear to be unlikely to cause adverse effects on populations of pelagic organisms.

In their responses to the CEPA Section 16 survey, two facilities reported releases of 2-butoxyethanol in liquid effluents to water bodies, but details of these releases are considered to be confidential business information. The effluents are treated before release and are considerably diluted in the receiving waters, where further biodegradation would occur. Concentrations of 2-butoxyethanol in the receiving waters would not likely be high enough to affect aquatic organisms.

3.1.2.3 Discussion of uncertainty

There are several sources of uncertainty in this environmental risk assessment. 2-Butoxyethanol was not included on the National Pollutant Release Inventory until 1999, so data on environmental releases of the substance in Canada before that year are not available. Few data were identified on environmental concentrations of 2-butoxyethanol in Canada or in other countries. The EEV for 2-butoxyethanol in air, 243 µg/m^3, is believed to be conservative, as the atmospheric concentration of the substance in the vicinity of an automotive plant in Windsor, Ontario, was only 7.3 µg/m^3. In view of the lack of monitoring data, the ChemCAN4 v. 0.95 model was used to estimate environmental concentrations of 2-butoxyethanol in the other environmental compartments (i.e., soil and water), based on the highest reported recent release of the substance in Canada, which occurred in 1996. To make a conservative estimate of environmental concentrations of 2-butoxyethanol, it was assumed, for modelling purposes, that all of this was released into southern Ontario. Kane (1993) compared measured environmental concentrations of five industrial chemicals and six pesticides with environmental concentrations estimated for the substances by the ChemCAN model. Sixty percent of the measured environmental concentrations were within one order of magnitude of predicted values, and 75% were within two orders of magnitude. The highest concentration of 2-butoxyethanol in 29 samples of Ontario drinking water was 5.0 µg/L, a value one order of magnitude below the ENEV. In the only relevant study identified from other countries, the concentration of 2-butoxyethanol in a polluted river in Japan ranged up to 5.68 mg/L, a value that is approximately the same as the CTV and two orders of magnitude above the ENEV. This study, however, was published in 1981.

No information was identified regarding the toxicity of 2-butoxyethanol to soil organisms or to terrestrial wildlife through atmospheric exposure. An estimation of a hazardous concentration to benthic species was the basis for the assessment of risk to soil organisms. The results of inhalation toxicity studies using laboratory strains of rats and mice were used for the assessment of risk to terrestrial biota. It is not possible to directly relate the results of these tests, changes in blood parameters indicative of hemolytic anemia, to the well-being of wildlife species. It is possible, however, that such changes in the blood could have some effect on the ability of wildlife to obtain food or to escape from predators. To account for these uncertainties, application factors were used in the environmental risk assessment to derive ENEVs.

Conservative risk quotients were small for all environmental assessment endpoints. Therefore, despite the data gaps regarding the environmental concentrations and effects of 2-butoxyethanol on soil organisms and terrestrial wildlife, the data available at this time are considered adequate for drawing a conclusion about the environmental risk of the substance in Canada.

3.2 CEPA 1999 64(b): Environment upon which life depends

2-Butoxyethanol does not deplete stratospheric ozone, and its potential for contributing to climate change is negligible. The potential of 2-butoxyethanol for photochemical ozone (smog) creation is moderate, but the low quantities of 2-butoxyethanol in the atmosphere are unlikely to make its contribution significant relative to that of other smog-forming substances.

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimates of potential exposure in humans

Available data on levels of 2-butoxyethanol in environmental media in Canada upon which estimates of population exposure may be based are limited to air and drinking water. These data are further limited by the lack of identification of reliable, quantitative, representative data on levels in residential indoor air, although available

TABLE 3 Estimated average intake of 2-butoxyethanol by six age groups in the general population

Route of exposure	Estimated average intake of 2-butoxyethanol by various age groups in the general population (µg/kg-bw per day)					
	0–6 months[1]	7 months–4 yrs[2]	5–11 yrs[3]	12–19 yrs[4]	20–59 yrs[5]	60+ yrs[6]
Ambient air[7]	0.3	0.6	0.5	0.3	0.2	0.2
Indoor air[8] (inhalation)	6.7	14	11	6.4	5.5	4.8
Drinking water[9]	0.02[10]	0.01	0.01	<0.01	<0.01	<0.01
Subtotal	**7.0**	**15**	**12**	**6.7**	**5.7**	**5.0**

[1] Assumed to weigh 7.5 kg, to drink 0.8 L of water per day, to breathe 2.1 m³ of air per day (EHD, 1998).

[2] Assumed to weigh 15.5 kg, to drink 0.70 L of water per day, to breathe 9.3 m³ of air per day (EHD, 1998).

[3] Assumed to weigh 31.0 kg, to drink 1.1 L of water per day, to breathe 14.5 m³ of air per day (EHD, 1998).

[4] Assumed to weigh 59.4 kg, to drink 1.2 L of water per day, to breathe 15.8 m³ of air per day (EHD, 1998).

[5] Assumed to weigh 70.9 kg, to drink 1.5 L of water per day, to breathe 16.2 m³ of air per day (EHD, 1998).

[6] Assumed to weigh 72.0 kg, to drink 1.6 L of water per day, to breathe 14.3 m³ of air per day (EHD, 1998).

[7] Intakes are estimated for inhalation only, based on the mean concentration of 2-butoxyethanol in samples of ambient air collected outside of 50 Canadian residences, 8.4 µg/m³ (Conor Pacific Environmental Technologies Inc., 1998). A concentration of 0.42 µg/m³ (one-half the detection limit of 0.84 µg/m³) was assumed for the samples in which 2-butoxyethanol was not detected. Each age group is assumed to spend an average of 3 hours per day outdoors.

[8] Intakes are estimated for inhalation only, based on the mean concentration of 2-butoxyethanol in 50 indoor air samples collected in Canadian residences, 27.5 µg/m³ (Conor Pacific Environmental Technologies Inc., 1998). A concentration of 0.42 µg/m³ (one-half the detection limit of 0.84 µg/m³) was assumed for the samples in which 2-butoxyethanol was not detected. Each age group is assumed to spend an average of 21 hours per day indoors.

[9] Based on the mean concentration of 2-butoxyethanol in drinking water in 50 drinking water samples collected at Canadian residences, 0.21 µg/L (detection limit 0.02 µg/L; frequency of detection 0.68) (Conor Pacific Environmental Technologies Inc., 1998). A concentration of 0.01 µg/L (one-half the detection limit of 0.02 µg/L) was assumed for the samples in which 2-butoxyethanol was not detected.

[10] Based on the assumption that infants were exclusively formula fed and consumed 800 ml of formula that was prepared with tap water (EHD, 1998).

Note: Insufficient data were available to estimate intake from soil or food.

information is sufficient to indicate that such levels are higher than those in ambient air.

Therefore, point estimates of average daily intakes (on a body weight basis) were derived primarily as a basis for determining the relative contributions to total intake by the few media for which relevant data were identified (Table 3). These point estimates were based on the limited data on mean concentrations in ambient air, indoor air and drinking water reported in the Canadian multimedia exposure study (Conor Pacific Environmental Technologies Inc., 1998) and reference values for body weight, inhalation volume and amount of drinking water consumed daily, for six age groups in the general population in Canada. Although confidence in the results of the multimedia exposure study is low, due to limitations of the analytical methodology (as described in Section 3.3.5), this is one of the only studies in which exposure in residential indoor air, the likely principal medium of exposure for the

general population (other than during the use of consumer products), was characterized; it is also the only investigation in which an attempt was made to characterize representative exposure of the Canadian general population. Mean concentrations in indoor air for this study, for which confidence in quantification is low, are similar to the single detected value for the only other identified investigation of a limited number of samples of residential indoor air in Italy, for which the limit of detection was not reported. Mean concentrations in the air in offices in well-documented studies in other countries were lower, although maximum concentrations were often higher (see Sections 2.3.2.2 and 2.3.2.3). The dermal uptake of 2-butoxyethanol from air can be estimated to be 0.47 µg/kg-bw per day using the following assumptions: an average permeability coefficient (K_p) of 3 cm/h (Corley *et al.*, 1997); exposure for 21 hours per day (EHD, 1998) to the average concentration of 2-butoxyethanol in indoor air (27.5 µg/m^3) from Conor Pacific Environmental Technologies Inc. (1998); an adult average total body surface area of 19 400 cm^2 (EHD, 1998); and an average adult body weight of 70.9 kg (EHD, 1998). This dermal uptake is roughly similar to the intake by inhalation of 2-butoxyethanol from ambient air containing an average concentration of 8.4 µg/m^3 (Conor Pacific Environmental Technologies Inc., 1998) for 3 hours per day (i.e., 0.2 µg/kg-bw per day for the adult age group in Table 3).

Since no monitoring data are available, it is not possible to determine the contribution of food to the overall intake of 2-butoxyethanol. However, 2-butoxyethanol is released primarily to air from industrial activities and through volatilization from consumer products and is unlikely to partition to food from air, based on its very low log K_{ow} (0.84), low bioconcentration factor and low Henry's law constant. Indeed, based on physical/chemical properties, the principal source of 2-butoxyethanol in food is likely to be water, for which reported concentrations are very low. (The solubility of 2-butoxyethanol is high, and it is predicted to remain in water if released or distributed to that medium.) In addition, if intake in food were estimated on the basis of concentrations predicted in terrestrial animals and plants by fugacity modelling, these values would be more than two orders of magnitude less than the estimated average intake from indoor air for an average adult, based on data from the multimedia exposure study. Exposure to 2-butoxyethanol in soil is likely to be negligible in comparison with that estimated for indoor air, based on its release patterns and the relatively small quantities ingested.

Direct exposure to 2-butoxyethanol via inhalation or dermal contact may also occur through use of a variety of consumer products containing the substance. Estimates of indoor air concentrations resulting from use of several cleaning products examined by Health Canada (Cao, 1999; Zhu *et al.*, 2001) were derived on the basis of emissions factors calculated from steady-state concentrations measured in emissions chambers. Assuming a standard room volume, a conservative air exchange rate and standard product use scenario information, estimated average concentrations of 2-butoxyethanol during the first 60 minutes following application range from 2.8 mg/m^3 for a glass cleaner to 62 mg/m^3 for an all-purpose spray cleaner (see Table 4).

Estimates of daily intake of 2-butoxyethanol via inhalation and dermal absorption associated with six common household cleaning tasks involving these spray and glass cleaners are also presented in Table 4. Because these products are used primarily by adults, estimated exposures have been derived for this age group only. (The differences in intake from a given medium among age classes, as a result of age-specific differences, would be small in relation to the variation in exposure from the various sources, in any case.) It is assumed that the hands become wetted by the cleaning products during performance of the various cleaning tasks. Dermal absorption from cleaning products was estimated using five different approaches, in order to characterize the variety of estimates that could be derived using the available data. The five

TABLE 4 Estimates of exposure to 2-butoxyethanol through inhalation and dermal uptake from use of household cleaning products

Product[1] identification	Task no.[2]	Concentration of 2-butoxyethanol		Average task duration[4] (hour/task)	Average task frequency[5] (tasks/day)	Estimated exposure per event (mg/task)		Estimated exposure (mg/kg-bw per day)	
		In product[3] (mg/cm³)	In room air[4] (mg/m³)			Dermal uptake[7]	Intake by inhalation[8]	Dermal uptake[9]	Intake by inhalation[9]
Spray cleaner #1	1	37.2	62	0.87	0.0329	36.4	70.1	0.017	0.032
	2			0.42	0.1316	25.3	33.8	0.047	0.063
	3			0.57	0.0658	29.5	45.9	0.027	0.043
	4			0.32	0.1316	22.1	25.8	0.041	0.048
	1–4			**all four tasks**		–	–	**0.132**	**0.186**
Spray cleaner #2	1	12.8	25	0.87	0.0329	12.5	28.3	0.006	0.013
	2			0.42	0.1316	8.7	13.6	0.016	0.025
	3			0.57	0.0658	10.1	18.5	0.009	0.017
	4			0.32	0.1316	7.6	10.4	0.014	0.019
	1–4			**all four tasks**		–	–	**0.045**	**0.074**
Glass cleaner #1	5	8.7	4.7	2.12	0.0109	14.8	13.0	0.002	0.002
	6			0.40	0.1316	5.8	2.4	0.011	0.004
	5–6			**both tasks**		–	–	**0.013**	**0.006**
Glass cleaner #2	5	5.0	2.8	2.12	0.0109	8.5	7.7	0.001	0.001
	6			0.40	0.1316	3.3	1.5	0.006	0.003
	5–6			**both tasks**		–	–	**0.007**	**0.004**

[1] These are among the household products purchased from retail outlets in Ottawa, Ontario, during 1998 and 1999 for emissions testing (Cao, 1999).

[2] Tasks typical of household cleaning activities are identified in U.S. EPA (1997) and include 1) clean outside of cabinets; 2) thoroughly clean counters; 3) clean bathroom or other tiled or ceramic walls; 4) clean outside of refrigerator and other appliances; 5) clean inside of windows; 6) clean other glass surfaces such as mirrors and tables.

[3] The 2-butoxyethanol content of each product was determined as a part of the emissions testing protocol (Cao, 1999).

[4] These concentrations are based on the emission factors determined by Cao (1999) and are calculated using an exponential decay model (Health Canada, 2001). Generic estimates of mass of product per task (i.e., 76 g/task for all-purpose spray cleaner and 17 g/task for spray glass cleaner) and of surface area cleaned per task (i.e., 4.5 m^2 for all-purpose spray cleaner and 2.3 m^2 for spray glass cleaner) are assumed (Versar Inc., 1986). A room volume of 17.4 m^3 and an air change rate of 0.5 per hour are also assumed.

[5] Average task durations expressed in minutes per event (U.S. EPA, 1997) are converted to durations in units of hour per task.

[6] Average task frequencies expressed in events per month (U.S. EPA, 1997) are converted to frequencies in units of task per day.

[7] These estimates of dermal uptake per event (i.e., per task) are developed using the non-steady-state approach outlined in U.S. EPA (1992). The estimated value of the permeability coefficient for 2-butoxyethanol from dilute aqueous solutions (i.e., 0.0014 cm/h) is used (based on the Potts and Guy [1992] correlation as cited in U.S. EPA [1992]). Values for the other parameters required for these calculations are from U.S. EPA (1992). The 2-butoxyethanol content of the product and the task duration are also used in each calculation. This approach results in the lowest estimates of dermal uptake among five approaches used in Health Canada (2001).

[8] Calculated by assuming an average adult breathing rate of 1.3 m^3/h, consistent with "light activity" (Allan, 1995; U.S. EPA, 1997), the concentration in room air shown in the table and the task duration, i.e., (mg/task) = (m^3/h) (mg/m^3) (h/task).

[9] Calculated as the product of the exposure per event times the event frequency divided by an assumed adult body weight of 70.9 kg (EHD, 1998).

approaches were as follows: (1) non-steady-state approach using measured permeability coefficient (K_p); (2) measured flux values; (3) steady-state approach using measured K_p; (4) non-steady-state approach using estimated K_p; and (5) 100% absorption from a thin film. (These were based on the methods recommended in U.S. EPA [1992], except for the latter, which was from Versar Inc. [1986]). The application of each of these approaches to the estimation of dermal absorption of 2-butoxyethanol from cleaning products is presented in detail in the health-related supporting documentation for this assessment (Health Canada, 2001). The estimates of dermal absorption presented in Table 4 of this Assessment Report are based on the non-steady-state approach with a K_p of 0.0014 cm/h, estimated using the Guy and Potts (1993) equation relating K_p to log K_{ow} and molecular weight; this approach was considered preferable in view of the fact that the lag times and/or time to steady state are not far removed from the durations for each of the tasks modelled and the limitations in the available measured data on dermal absorption of 2-butoxyethanol.[a] The estimated K_p was within the same order of magnitude as the measured K_p based on an *in vivo* study in guinea pigs exposed dermally to 2-butoxyethanol solutions (Johanson and Fernström, 1988), and within a factor of five of both the estimated and measured values reported in U.S. EPA (1992) for 2-ethoxyethanol, a structurally similar compound. The estimated dermal absorption derived by the various approaches is fairly similar in any case, differing by 9- to 32-fold across all of them, depending on the cleaning product modelled.

The estimated overall daily intakes (i.e., intakes from all tasks combined) via inhalation range from 0.074 to 0.186 mg/kg-bw per day for all-purpose spray cleaners and from 0.004 to 0.006 mg/kg-bw per day for spray glass cleaners, assuming that the user is exposed only for the task duration, average frequency of use, standard values for breathing rate consistent with "light activity" and average adult body weight. (Note that these estimates assume that aerosol generated as overspray is not inhaled by the user and that additional inhalation of background concentrations of 2-butoxyethanol in the residential air following the cleaning activities are relatively low compared with the higher intakes during active use of the products.) Dermal absorption during the performance of these tasks could contribute an additional 0.045–0.132 mg/kg-bw per day for the all-purpose cleaners and 0.007–0.013 mg/kg-bw per day for the glass cleaners, assuming contact with the palms of both hands and an estimated K_p of 0.0014 cm/h and applying a non-steady-state approach. Based on these estimated values, therefore, both inhalation and dermal absorption contribute significantly to intake of 2-butoxyethanol during use of domestic products containing the substance.

It should be noted that estimates of exposure to 2-butoxyethanol through use of consumer products were developed only for a few of the small number of products that were investigated by Health Canada, and that exposure to the substance could also occur during use of a variety of other types of products, as described in Section 2.3.2.9. Little information was identified in the literature regarding measured human exposures from consumer products. Norbäck *et al.* (1995, 1996) reported that personal air samples collected in the breathing zone of Swedish house painters using water-based paints under "normal" working conditions contained a mean concentration of 59 µg 2-butoxyethanol/m^3 (maximum 730 µg/m^3). Concentrations were below levels of detection in personal air and area samples (i.e., <3.4 and <1.0 mg/m^3, respectively) for cleaners at a school in Australia using a

[a] The first three approaches, which were based on the K_p of 0.012 cm/h measured in an *in vivo* study in guinea pigs exposed dermally to 5% and 10% solutions of 2-butoxyethanol (Johanson and Fernström, 1988), were considered less suitable approaches with which to estimate dermal absorption as a consequence of their high variability, lack of dose–response and/or the substantially higher solution concentrations used in this study compared with the cleaning products being modelled.

diluted solution of a product containing 1% 2-butoxyethanol (National Industrial Chemicals Notification and Assessment Scheme, 1996). Office window cleaners in France were exposed to <0.3–0.7 ppm 2-butoxyethanol (<1.5–3.4 mg/m^3) during use of spray cleaners containing 0.9 or 9.8% of the substance (Vincent *et al.*, 1993).

3.3.2 Human health hazard characterization

Few data were identified on the potential effects of 2-butoxyethanol in humans. Although effects on the blood have been observed in exposed workers and in several cases of incidental exposure (Rambourg-Schepens *et al.*, 1988; Gijsenbergh *et al.*, 1989; Bauer *et al.*, 1992; Haufroid *et al.*, 1997), due to limitations of these studies, characterization of health hazards associated with 2-butoxyethanol is based primarily on studies in experimental animals.

3.3.2.1 Hematological effects

The majority of toxicological investigations with 2-butoxyethanol have been conducted in rats, in which the most sensitive target tissue is the blood. Alterations in hematological parameters characteristic of hemolytic anemia have been observed in this species following acute, short-term, subchronic or chronic exposure to 2-butoxyethanol via inhalation, ingestion or dermal application (Carpenter *et al.*, 1956; Dodd *et al.*, 1983; Bartnik *et al.*, 1987; Ghanayem *et al.*, 1987; NTP, 1989) In some of these studies, the effects appeared to be reversible after cessation of exposure, as the severity of the hematological changes decreased with increasing time since exposure (Grant *et al.*, 1985; Krasavage, 1986; NTP, 1989; Ghanayem *et al.*, 1992). Similarly, tolerance, or autoprotection, was suggested by the results of two studies in which the hematological effects were less severe in rats that had been exposed to 2-butoxyethanol prior to administration than in rats receiving only the subsequent doses, although the protective effect declined with increasing time between exposures. In addition, bleeding rats prior to acute exposure to 2-butoxyethanol reduced the severity of the hematotoxicity (Ghanayem *et al.*, 1992; Sivarao and Mehendale, 1995). These data suggest that older red blood cells are more susceptible to 2-butoxyethanol-induced effects (which has also been demonstrated in *in vitro* studies); as they are replaced by more resilient younger cells, the severity of the hematotoxic response declines.

However, such reversibility or autoprotection is likely limited, since it was not observed in rats repeatedly exposed to 2-butoxyethanol for longer durations. In rats exposed to 2-butoxyethanol in the drinking water for 13 weeks, symptoms of regenerative hemolytic anemia were still present at the end of the study in females at all doses tested (NTP, 1993). Similar effects were also noted in the same strain of rats exposed via inhalation for 14 weeks to 2-butoxyethanol at all concentrations tested, based on results of studies conducted by the NTP (1998). The anemia was considered to be macrocytic, normochromic and responsive. Other indicators of regenerative anemia, including increased hematopoiesis, hemosiderin accumulation in the liver and kidney and bone marrow hyperplasia, were also observed in both sexes; thrombosis, likely associated with severe acute hemolysis, was also noted in females at the higher exposure levels. In addition, in the chronic study conducted by the NTP (1998), in which rats were exposed to 2-butoxyethanol by inhalation for up to 2 years, hemolytic anemia was evident in animals monitored at regular intervals up to 12 months. The anemia, which was again characterized as macrocytic, normochromic and responsive, was observed at all concentrations; the severity of the effects increased with exposure level and did not ameliorate significantly over time.

2-Butoxyethanol-induced hematological effects have also been observed in other species of experimental animals. In mice, a decrease in red blood cell count was noted following short-term oral exposure (Nagano *et al.*, 1979, 1984), while alterations in hematological parameters were

reported in subchronic and chronic inhalation studies (NTP, 1998), although, as discussed above, mice appear to be less sensitive than rats to 2-butoxyethanol-induced hematotoxicity. Hematological effects were also noted in limited short-term studies in rabbits, dogs and monkeys (Carpenter *et al.*, 1956; Truhaut *et al.*, 1979; Union Carbide, 1980; Tyl *et al.*, 1984), although available data are inadequate to allow differences in species sensitivity to be evaluated. In general, these effects were observed only at doses greater than those that induced similar, more severe effects in rats.

There is also some evidence that the blood is a sensitive target tissue in the developing young following *in utero* exposure to 2-butoxyethanol in both rats and mice. Hematological effects were reported in the fetuses of rats exposed to doses of 2-butoxyethanol that were also hematotoxic in the dams (NTP, 1989), while an increase in fetal mortality in mice (Heindel *et al.*, 1990) has been hypothesized to be due to hydrops foetalis, associated with severe anemia induced by 2-butoxyethanol or its metabolite, BAA, transported across the placenta (Atkins, 1999); however, no description of the possible cause of fetal death was presented in the report of this study.

In view of the extensive database that indicates that 2-butoxyethanol is hematotoxic in multiple experimental species and the limited evidence of changes in hematological parameters in occupationally and incidentally exposed humans, 2-butoxyethanol is considered likely to be hematotoxic in humans. Although limited, available data from toxicokinetic studies and comparative *in vitro* investigations suggest that humans may be less sensitive to 2-butoxyethanol-induced hematotoxicity than rats (although few data were identified on inter-individual sensitivity in humans), which, at least based on the results of *in vivo* studies, appear to be the most sensitive of the animal species investigated.

3.3.2.2 Other non-neoplastic effects

Other target organs of 2-butoxyethanol-induced effects in various species (rats, mice, rabbits or guinea pigs) following acute, short-term or long-term exposure (Carpenter *et al.*, 1956; Truhaut *et al.*, 1979; Krasavage, 1986; Bartnik *et al.*, 1987; Ghanayem *et al.*, 1987; NTP, 1993, 1998) include the liver, kidney, spleen and bone marrow. Many of the observed effects, such as accumulation of hemosiderin pigment, increased hematopoiesis and cellularity, and hemoglobinuria, are considered to be secondary or in response to hemolytic anemia (NTP, 1998), while other effects, such as alterations in relative organ weights and some histopathological changes, occurred only at doses that were also hemolytic. Although cytoplasmic changes were noted in the liver of male rats exposed subchronically to oral doses lower than those that induced alterations in blood parameters (although these doses were hematotoxic in females), these effects may have been related to induction of enzymes involved in metabolism of 2-butoxyethanol (NTP, 1993).

The forestomach was also a critical target for 2-butoxyethanol-induced toxicity in mice. In the chronic study in mice, increased incidences of inflammation, epithelial hyperplasia and/or ulceration were noted at all concentrations tested (with females being more sensitive than males) following inhalation, with some evidence of concentration-related trends in incidence and severity of forestomach lesions in female mice; these effects were also observed in both mice and rats subchronically exposed to higher concentrations that also induced hematological changes (NTP, 1998). These effects on the forestomach are also in concordance with neoplastic lesions at this site in mice. Relevant data with which to quantitatively address possible interspecies variations in sensitivity to these effects were not identified.

In investigations of the potential developmental toxicity of 2-butoxyethanol in rats, mice or rabbits, embryotoxic or fetotoxic effects or malformations have generally been observed only at or above doses that are also maternally toxic (Hardin *et al.*, 1984; Schuler *et al.*, 1984; Wier *et al.*, 1987; NTP, 1989; Heindel *et al.*, 1990). Similarly, effects on female reproductive ability or on male and female reproductive organs

(some of which were not considered to be of biological significance) were observed only at doses or concentrations that were associated with high mortality or that were greater than those that induced hematotoxicity (Heindel *et al.*, 1990; NTP, 1993, 1998).

Based on limited data, 2-butoxyethanol does not appear to induce immunological effects at doses lower than those associated with hematotoxicity or other adverse effects (Exon *et al.*, 1991; Smialowicz *et al.*, 1992). Data on the potential effects of 2-butoxyethanol on the nervous system are insufficient for evaluation.

3.3.2.3 Carcinogenicity and genotoxicity

In the chronic bioassays conducted by the NTP (1998), incidences of tumours were significantly increased (often only marginally) only at the higher concentrations tested (in some cases only when compared with historical controls). There is some indication that neoplasms at one site (i.e., the forestomach) represent a progression from non-neoplastic effects associated with local inflammation and response. Although the potential relation between these lesions was not investigated, it was ascertained that induction of tumours at this site did not involve mutations of the H-*ras* oncogene (codon 61), based on examination of mutational spectra in tumours of exposed and control mice. While it was concluded that there was some evidence of carcinogenicity in mice (based on increased incidences of hemangiosarcomas of the liver in males and squamous cell papillomas of the forestomach in females), the evidence in female rats was considered only equivocal (based on a marginal increase in the incidence of benign or malignant pheochromocytomas of the adrenal gland). Information on the mode of induction of these tumours was not identified.

The apparent low carcinogenic potency of 2-butoxyethanol is in concordance with equivocal evidence that 2-butoxyethanol may be weakly genotoxic *in vitro*. The observations that 2-butoxyethanol did not induce DNA adducts at several sites in exposed rodents but did induce mitotic division aberrations/aneuploidy (possibly due to interference with spindle formation) and inhibit intercell communication would support the hypothesis that the induction of these tumours may not involve direct interaction of 2-butoxyethanol with genetic material. However, positive or equivocal results were obtained for induction of other genetic endpoints by the parent compound and its metabolites. In addition, 2-butoxyethanol did not promote initiated cells in a transgenic mouse assay (Keith *et al.*, 1996). Therefore, on the basis of limited evidence of carcinogenicity in rodents and genotoxicity in *in vitro* assays, for which the potency appears to be low, 2-butoxyethanol is considered to be possibly weakly carcinogenic in humans.

3.3.3 Exposure–response analyses

Based on available data, inhalation in indoor air is an important route of exposure to 2-butoxyethanol for the general population, particularly for those using consumer products that contain the substance. Since intake in food is highly uncertain (relevant monitoring data have not been identified) but is expected to be low, as levels in water, the likely principal source in food, are low, exposure–response relationships for health effects associated with 2-butoxyethanol have been quantified for the inhalation route only.

In view of the sufficient weight of evidence for the hematotoxicity of 2-butoxyethanol, in short- and long-term studies in experimental animals (with the lowest LOEL being 31.2 ppm [151 mg/m^3]), Benchmark Concentrations (BMCs) for a variety of hematological endpoints were derived on the basis of the long-term studies in animals in which adequate exposure–response data were presented.

Although considered to be secondary to hemolytic anemia, BMCs were also derived on the basis of the incidence of hemosiderin pigmentation of chronically exposed rodents, since this effect was also observed in rats and mice at concentrations as low as 31.2 ppm; these BMCs are derived as a discrete measure of

2-butoxyethanol-induced effects, primarily for comparison with those based on the continuous data for hematological parameters.

Although less consistently observed, the forestomach was also a sensitive target organ in rodents exposed to 2-butoxyethanol via inhalation, with non-neoplastic effects being induced in a chronic study in mice at the lowest concentration investigated (62.5 mg/m^3) and at higher concentrations in a subchronic study in rats (≥250 ppm [≥1208 mg/m^3]). Prolonged exposure to 2-butoxyethanol at concentrations of 250 ppm (1208 mg/m^3) or more was also associated with a significant increase in the incidence of tumours in the forestomach of mice. Therefore, a BMC and a Tumorigenic Concentration were derived for non-neoplastic and neoplastic effects on the forestomach, respectively.

Marginal, but statistically significant, increases in the incidence of other tumours, including hemangiosarcomas of the liver as well as hepatocellular carcinomas, were also observed in male mice at the highest concentration of 2-butoxyethanol (i.e., 250 ppm [1208 mg/m^3]) (NTP, 1998). Therefore, although the weight of evidence for an association with exposure to 2-butoxyethanol is very limited, Tumorigenic Concentrations have been derived for these effects, primarily for comparison with values derived for other endpoints.

Based on the available data from short- and long-term studies in various experimental species and *in vitro* investigations in blood cells from animals and humans, as well as information on toxicokinetics and metabolism of 2-butoxyethanol, rats appear to be more sensitive to the hematotoxic effects induced by the substance than other species. Variations in sensitivity to 2-butoxyethanol-induced hematotoxicity are well correlated with variations in production and clearance of BAA. These observations as well as additional studies in which oxidation of 2-butoxyethanol to BAA is inhibited indicate that the acetic acid metabolite is principally responsible for hematological effects associated with 2-butoxyethanol. The major pathways of metabolism and disposition of 2-butoxyethanol are qualitatively similar in rats, mice and humans, with BAA being a major circulating metabolite in all species and being eliminated primarily by renal excretion. However, while there is considerable evidence that BAA is the putatively toxic entity, and hence an appropriate surrogate for interspecies and intraspecies (interindividual) adjustment for the toxicokinetic component of the uncertainty factor for a Tolerable Concentration (TC) for critical hematological effects (i.e., hemolysis), the relevance of the systemic disposition of BAA to lesions of the forestomach in mice is unknown. Therefore, values for these two effects have been developed separately here, with inclusion of compound-related adjustment factors for which data are sufficient for one (hemolysis in rats) but not the other (forestomach lesions in female mice).

3.3.3.1 Hematological effects

The studies considered most appropriate for derivation of BMCs for use in characterizing the risk of hematological effects in human health associated with exposure to 2-butoxyethanol in the environment are those conducted by the NTP (1998), in which rats and mice were exposed to the substance for up to 2 years. In addition, the lowest effect levels for these endpoints were derived from these studies. In these investigations, groups of up to 50 male or female F344/N rats were exposed to concentrations of 0, 31.2, 62.5 or 125 ppm (0, 151, 302 or 604 mg/m^3) for 6 hours per day, while similar groups of B6C3F$_1$ mice were exposed to concentrations of 0, 62.5, 125 or 250 ppm (0, 302, 604 or 1208 mg/m^3). Various hematological parameters in 10 animals per exposure group were measured at several time points throughout the first 12 months of exposure. Statistically significant changes in several parameters were noted at these intervals in both species; therefore, BMC_{10}s were calculated for these effects, as described below. The parameters selected for exposure–response analysis were those for which there were significant changes

at lowest exposure levels and for which there was some indication of a concentration-related trend. BMC_{05}s are presented here only for measurements made at the latest time point (i.e., 12 months), although for those parameters for which there were significant changes at earlier time points, BMC_{05}s were also calculated, for examination of the influence of duration on the estimates of potency.

For these hematological parameters (i.e., continuous endpoints), the BMC_{05} is defined as the concentration associated with a 5% increase in the absolute risk of seeing an "adverse" response. This method utilizes the "hybrid" method of Crump (1995) to define an adverse response as the response at which 5% of the control group would be abnormal. The probability of an adverse response is then modelled, as opposed to modelling the mean response. The advantage to this method is that the BMC_{05} may be calculated using the same formula as that used for discrete data.

The Weibull model was fit to each of the endpoints using BENCH_C (Crump and Van Landingham, 1996):

$$P(d) = p_0 + (1 - p_0)\left[1 - e^{-\beta d^k}\right]$$

where d is dose, $P(d)$ is the probability of an adverse response at dose d, and k, β and p_0 are parameters to be estimated. The BMC_{05} was then calculated as the concentration C such that

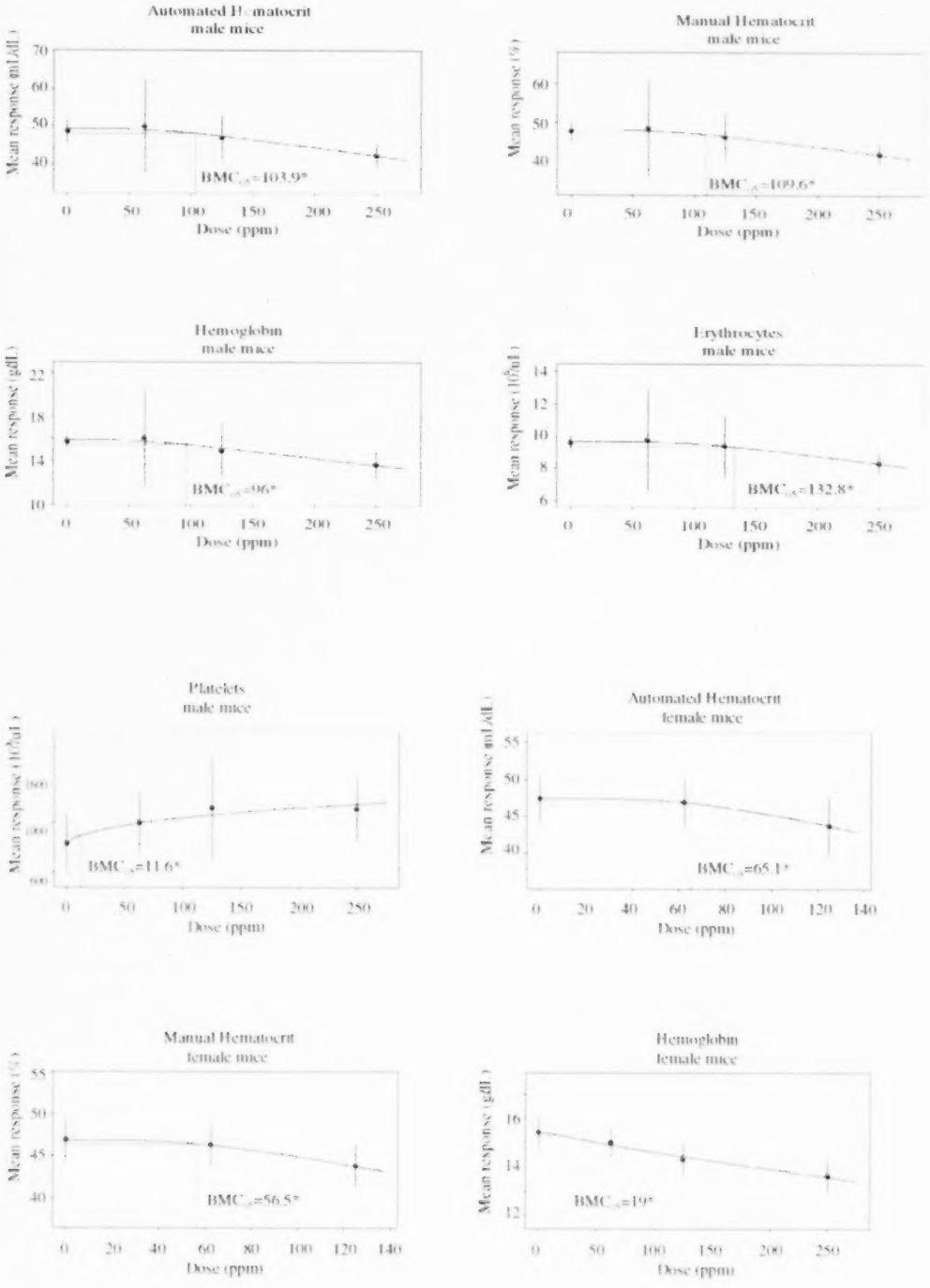
$$P(C) - P(0) = 0.05$$

Plots of the data and fitted curves are in Figure 1. Lack of fit of the model was assessed by an F-test. A p-value less than 0.05 indicates lack of fit. BMC_{05}s and the results of model fitting are displayed in Tables 5 (mice) and 6 (rats). Although the BMC_{05}s were derived on the basis of studies in which animals were exposed for a duration of less than lifetime, it was not considered appropriate to amortize exposure over a 2-year period (as is done for many chronic effects), in view of the shorter time course for formation, aging and elimination of blood cells. Values were adjusted, however, to account for non-continuous exposure of only 6 hours per day and 5 days per week by multiplying by 6/24 × 5/7 (adjusted values presented in tables).

For female mice, the model showed lack of fit for manual and automatic hematocrit and for erythrocytes. Including a threshold did not improve the model fit, so the top exposure group was eliminated. This doubled the estimated BMC_{05} for each endpoint but reduced to zero the degrees of freedom for assessing lack of fit. The model passes exactly through each of the data points, so even though a lack of fit test cannot be performed, the fit is "perfect." For rats, data for only three exposure groups were available, so the model passed directly through the data points, resulting in an F-statistic of zero and a p-value of 1.

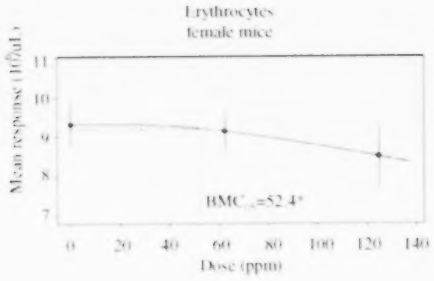
As presented in Tables 5 and 6, the BMC_{05}s for hematological effects range from 1.1 to 13.2 ppm (5.3 to 63 mg/m^3) in rats and from 2.1 to 23.7 ppm (10 to 115 mg/m^3) in mice. In rats, the most sensitive endpoint, based solely on these estimates of potency, is the increase in mean cell hemoglobin, while in mice, the lowest BMC_{05} was that derived for increased platelets. In general, the BMC_{05}s for each parameter are lower for rats than they are for mice (although there are some exceptions in females), consistent with the observation that statistically significant changes were observed at lower concentrations in rats than in mice. Similarly, BMC_{05}s were generally lower in female rats than in male rats, which correlates with observed differences in clearance of the putatively active metabolite, BAA, in females, along with the fact that significant changes appeared earlier in females. In addition, although not presented here, BMC_{05}s determined based on measurements made at 3 and 6 months of exposure are lower in female rats than in male rats.

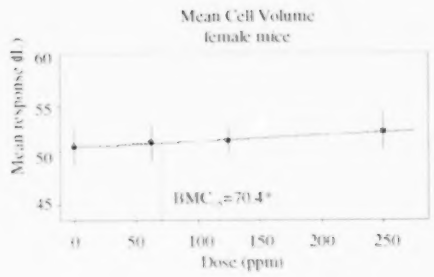
FIGURE 1 Exposure–response curves for hematological effects in mice and rats

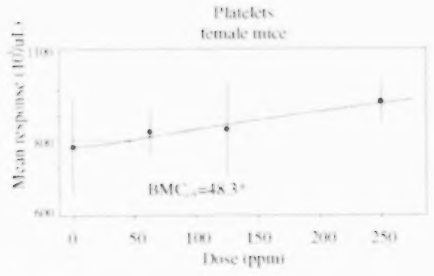


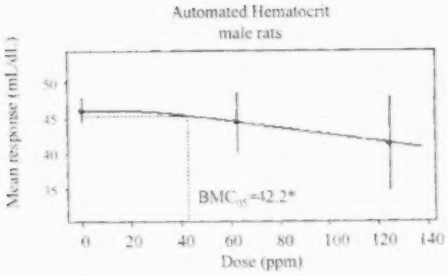
* BMC$_{1.4}$ unadjusted for non-constant dosing

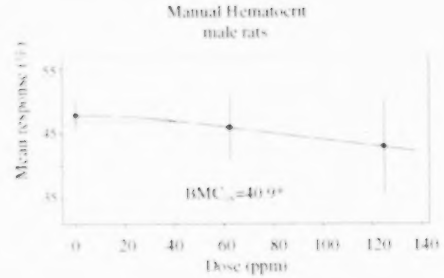
FIGURE 1 (continued)

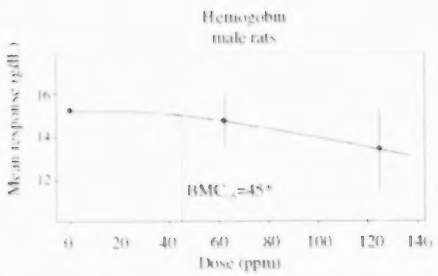


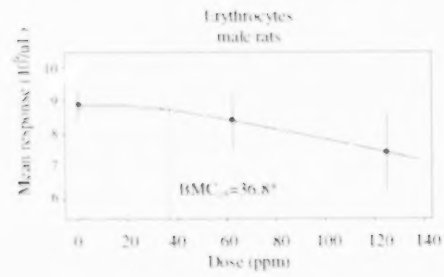


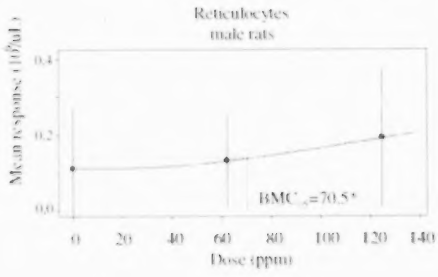






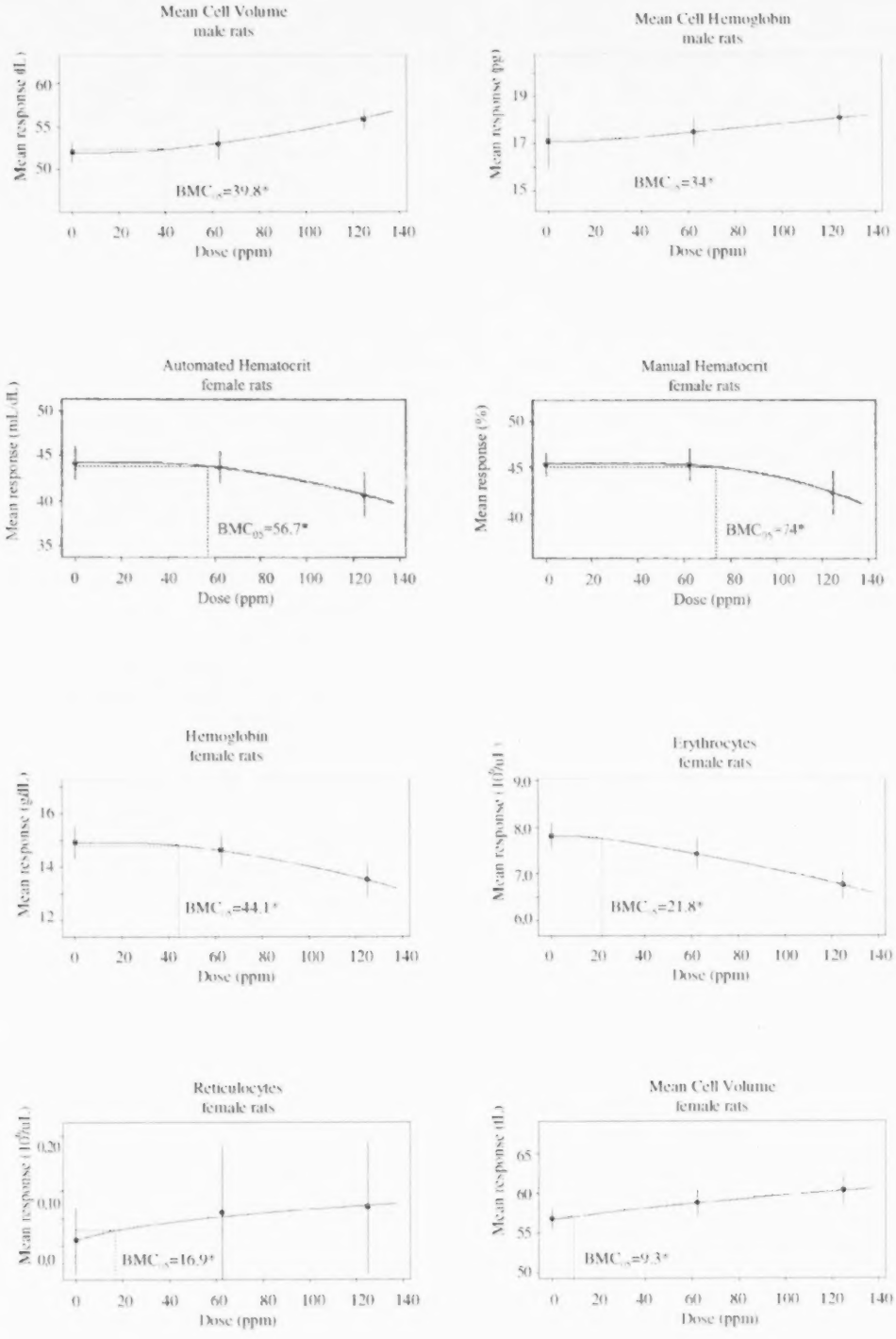






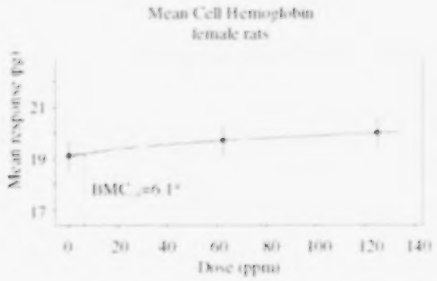
* BMC_{10} unadjusted for non-constant dosing

FIGURE 1 (continued)



* BMC_{05} unadjusted for non-constant dosing

FIGURE 1 (continued)



* BMC$_{10}$ unadjusted for non-constant dosing

A TC was developed on the basis of the BMC$_{10}$s for hematological effects in rats, quantitatively taking into account interspecies variations in kinetics and dynamics.

There are two published physiologically based pharmacokinetic (PBPK) models in which uptake and metabolism of 2-butoxyethanol as well as circulating concentrations and renal limination of BAA are included — namely, those of Corley *et al.* (1994) and Lee *et al.* (1998). Scaling of the models to humans was largely based on adjustment by (body weight)$^{0.7}$ of metabolic parameters and appropriate physiologically based differences in organ weights and organ blood flow; these values were taken from the literature or determined either experimentally or by fitting simulations to experimental data. The Corley *et al.* (1994, 1997) model included lung, rapidly and slowly perfused tissues, fat, skin, muscle, gastrointestinal tract and liver for both 2-butoxyethanol and BAA. In the latter version of the model, Corley *et al.* (1997) set the metabolism to non-BAA products to zero and included variable skin blood flow and human data on dermal absorption of vapour. The model of Lee *et al.* (1998) included separate compartments for kidney and spleen; muscle was included in the compartment for slowly perfused tissue. Corley *et al.* (1994, 1997) improved the fit slightly for older rats by increasing the volume of the fat compartment and by decreasing the renal elimination rate, both of which are considered common changes in aging rats. The Lee *et al.* (1998) model was also designed to describe the toxicokinetics of 2-butoxyethanol and BAA in different species following repeated long-term exposure and incorporated adjustments to account for differences in male versus female rats and age-related changes and to better simulate data in mice. For both models, simulated levels of 2-butoxyethanol and BAA in human blood, as well as concentrations of BAA in the urine, fit reasonably well with data presented in investigations of the toxicokinetics of 2-butoxyethanol in humans (e.g., Johanson, 1986, 1988; Johanson and Johnsson, 1991).

However, there are a number of untested assumptions that contribute to uncertainty in use of the model in interspecies scaling and high dose to low-dose extrapolation. In order to minimize the number of parameters requiring experimental validation, renal elimination of BAA is assumed to be by saturable renal tubular secretion and limited by plasma protein binding. While available data support the secretion of BAA by the rat kidney (Grant *et al.*, 1997), the models do not appear to allow for simple glomerular filtration of non-protein-bound BAA and, more importantly, do not include any consideration of the potential for pH-dependent reabsorption from the renal tubule. The latter may well explain the apparent dose dependency in the elimination of

TABLE 5 BMC_{05}s and model fitting information for hematological effects in mice

	BMC_{05} (ppm)	95% LCL (ppm)	F statistic	df	p-value
Male mice					
Automated hematocrit	18.6	9.1	1.13	1,35	0.30
Manual hematocrit	19.6	8.9	0.51	1,35	0.48
Hemoglobin	17.1	7.2	0.88	1,35	0.35
Erythrocytes	23.7	9.4	0.19	1,35	0.66
Platelets	2.1	1.0	1.89	1,35	0.18
Female mice					
Automated hematocrit[1]	11.6	6.1	0	0,36	1.00
Manual hematocrit[1]	10.1	5.3	0	0,36	1.00
Hemoglobin	3.4	1.6	2.54	1,36	0.12
Erythrocytes[1]	9.4	4.9	0	0,36	1.00
Mean cell volume	12.6	2.4	0.34	1,36	0.56
Platelets	8.6	1.9	1.82	1,36	0.19

[1] Highest dose group excluded to eliminate downturn from dose–response relationship.

BAA, if accumulation of this metabolite were to lead to a metabolic acidosis, which would then reduce its renal elimination.

Use of output of the models as an appropriate basis for interspecies scaling of the toxicokinetic component of adjustment factors for development of the TC is justified, primarily, therefore, on the basis of their mathematical validation. In fact, due to the non-validated simplifying biological assumptions inherent in the models, particularly in relation to the renal handling of the key metabolite, BAA, they are considered to add little additional value to scaling of basic kinetic parameters, such as area under the curve (AUC) or clearance, by (body weight)$^{0.7}$. Hence, a simple comparison of the AUCs for humans and experimental animals for the active metabolite is as informative for interspecies scaling.

The relevant surrogate for hematological effects is considered to be the AUC of the concentration–time relationship for the putatively toxic metabolite, BAA, since there is some evidence that duration of exposure is important and since this approach is more conservative. Interspecies scaling is based, in part, on relevant data from the study in human volunteers of Johanson and Johnsson (1991). In this investigation, concentrations of BAA in blood of five healthy male human volunteers (ages not specified) were determined at 0, 2, 4 and 6 hours before and following a 2-hour exposure to 2-butoxyethanol by inhalation. Data reported in this investigation that are relevant to determination of the AUC were that the BAA level peaked after 2–4 hours and that peak concentrations were 36–46 µM (average 41) in three subjects after 2 hours and 52–60 µM (average 56) in two subjects after 4 hours; the average half-time in blood was 4.3 hours. The tabulated mean data were analysed using a non-compartmental model and a standard kinetic program (WinNonLin) which gave an AUC of 230 µM·h to 7.1 hours, a terminal half-life of 4.5 h and an AUC extrapolated to infinity of 414 µM·h. Since these relate to a 2-hour exposure to 20 ppm (97 mg/m^3), the AUC is 414/(2 × 20) = 10.4 µM·h/ppm·h. Adjustment of this value to account for working versus resting

TABLE 6 BMC_{05}s and model fitting information for hematological effects in rats

	BMC_{05} (ppm)	95% LCL (ppm)	F statistic	df	p-value
Male rats					
Automated hematocrit	7.6	1.6	0	0,23	1.00
Manual hematocrit	7.3	1.1	0	0,23	1.00
Hemoglobin	8.0	3.7	0	0,23	1.00
Erythrocytes	6.6	2.8	0	0,23	1.00
Reticulocytes	12.6	2.1	0	0,23	1.00
Mean cell volume	7.1	4.6	0	0,23	1.00
Mean cell hemoglobin	6.1	1.6	0	0,23	1.00
Female rats					
Automated hematocrit	10.1	6.2	0	0,23	1.00
Manual hematocrit	13.2	8.1	0	0,23	1.00
Hemoglobin	7.9	5.0	0	0,23	1.00
Erythrocytes	3.9	2.3	0	0,23	1.00
Reticulocytes	3.0	1.1	0	0,23	1.00
Mean cell volume	1.7	0.27	0	0,23	1.00
Mean cell hemoglobin	1.1	0.23	0	0,23	1.00

conditions[*] (for comparison with the AUC in rats) (12.5 m^3/day + 47.5 m^3/day to account for ventilation rate at 50 W work versus resting conditions), the AUC is 2.73 μM·h/ppm·h. Based on the Corley *et al.* (1997) model for humans for which predicted levels of BAA in arterial blood more closely simulated the reported data of Johanson and Johnsson (1991), the predicted AUC for 50 W activity is similar (411 μM·h at 24 hours and 420 μM·h when extrapolated to 7 days), while that for at rest is 102 (i.e., the ratio between these predicted values is comparable to the ratio between ventilation rates used to adjust for working versus resting conditions).

The most appropriate study on which to base the comparative measure of the surrogate for scaling of that portion of the adjustment factor that addresses interspecies toxicokinetic variation is the investigation of Dill *et al.* (1998), in which groups of 16 male and female F344 rats (the same strain as that in the critical investigation on which the BMCs are based) were exposed to 31.2, 62.5 or 125 ppm (151, 302 or 604 mg/m^3) and 62.5, 125 or 250 ppm (302, 604 or 1208 mg/m^3), 6 hours per day, 5 days per week, respectively, for up to 18 months. Post-exposure blood samples were collected at 1 day, 2 weeks and 3, 6, 12 and 18 months; post-exposure 16-hour urine samples were collected at 2 weeks and 3, 6, 12 and 18 months of exposure. AUCs in this study were reported for the post-exposure period only. Hence, the AUC in animals was modelled on the basis of the PBPK model of Lee *et al.* (1998) by integrating the concentration of BAA in venous blood at 62.5 ppm for an inhalation time of 6 hours with a stop time of 24 hours. The resulting value was 2077.5 μM·h/(62.5 ppm·6h) = 5.54 μM·h/ppm·h. This result is consistent with the AUC in the post exposure period reported

[*] Such adjustment is considered appropriate in view of the high solubility of 2-butoxyethanol in blood.

by the authors, being approximately twice the reported latter value.

The resulting ratio between the AUC for humans and that for rats is 2.73/5.54 or 0.5, compared with the default value for this component of 4. However, although the data on toxicokinetics in humans (restricted to five male volunteers) are sufficient as a basis for determination of a measure of central tendency for interspecies comparison, they are inadequate to inform the intraspecies (interindividual) toxicokinetic component of the uncertainty factor, which reverts to default.[8]

Information relevant to consideration of both the interspecies and intraspecies (interindividual) dynamic components of uncertainty/adjustment factors is available from several studies in which the direct effects of BAA on several measures of hemolysis in rat and human erythrocytes have been examined *in vitro* (i.e., Bartnik *et al.*, 1987; Ghanayem, 1989; Udden, 1994; Udden and Patton, 1994), as discussed above in Section 2.4.3.10. Based on these investigations, there is consistent evidence that human erythrocytes are at least 10-fold less sensitive than rat erythrocytes; therefore, the default factor for the interspecies component for dynamics (2.5) can be replaced with a value of 0.1 (and this would still be conservative). It is noteworthy that the endpoints in these studies on which this adjustment is based (hematocrit and hemoglobin concentration) are consistent with some of the endpoints in *in vivo* studies for which TCs were lowest. However, available data on intraspecies (interindividual) variation in dynamics are limited primarily to one study *in vitro* in blood from various potentially sensitive subgroups of the population (i.e., seniors and patients with sickle cell disease and spherocytosis) in which no response was observed at the administered concentration (n = 9, 9, 7 and 3) (Udden, 1994). In several other studies, hemolysis was examined in generally pooled blood samples from unspecified or very small numbers of individuals (n = 3) as a basis solely for estimation of the central tendency for interspecies comparison (Bartnik *et al.*, 1987; Ghanayem, 1989; Udden and Patton, 1994). These data are inadequate to meaningfully quantitatively inform the replacement of default with a data-derived adjustment factor; hence, the default value of 3.2 is maintained.

The total compound-specific adjustment/uncertainty factor is, therefore, 0.5 (interspecies, toxicokinetic) × 0.1 (interspecies, toxicodynamic) × 3.2 (intraspecies, interindividual toxicokinetics) × 3.2 (intraspecies, interindividual toxicodynamics) = 0.5.

Based on the above considerations regarding relative sensitivity to 2-butoxyethanol-induced hematotoxicity, the TC has been derived as follows:

$$TC = \frac{5.3\ mg/m^3}{0.5}$$

$$\cong 11\ mg/m^3$$

where:

- 5.3 mg/m^3 is the lower end of the range of BMCs for hematological effects in the long-term study in rats (NTP, 1998), and
- 0.5 is the compound-specific uncertainty/adjustment factor described above.

While limitations of the monitoring data in the single identified relevant cross-sectional study of workers preclude its utility in bounding the TC developed on the basis of studies in animals, the value developed above is protective,

[8] For example, there is a well-recognized genetic polymorphism for alcohol dehydrogenases (the group of enzymes responsible for the first step in the metabolism of 2-butoxyethanol, i.e., oxidation to 2-butoxyaldehyde); however, while this is relevant to replacement of default for interindividual variation, the proportion of the population affected is sufficiently small (i.e., 5%) that it would not meaningfully impact on the measure of central tendency. Variants of alcohol and aldehyde dehydrogenase common in the Oriental population would decrease the rate of metabolism to the active compound and hence reduce risk (Agarwal and Goedde, 1992; Goedde and Agarwal, 1992).

based on the early, shorter-term clinical study (Carpenter *et al.*, 1956).

3.3.3.2 Other (non-hematological) effects

BMC_{05}s were derived for other non-cancer effects, including Kupffer cell pigmentation of the liver (although considered secondary to hemolysis), as well as ulceration and hyperplasia of the forestomach (all severities combined), based on the observations in rats and mice exposed to 2-butoxyethanol for up to 2 years (NTP, 1998). For such discrete endpoints, the BMC_{05} is defined as the concentration of the substance associated with a 5% increase in incidence over background response rate. It is calculated by first fitting the following model to the exposure–response data (Howe, 1995):

$$P(d) = q_0 + (1 - q_0) \cdot \left[1 - e^{-q_1 d - \cdots - q_k d^k}\right]$$

where d is dose, k is the number of dose groups in the study, $P(d)$ is the probability of the animal developing the effect at dose d, and $q_i > 0$, $i = 0,\ldots,k$ are parameters to be estimated.

The models were fit to the incidence data using THRESH (Howe, 1995), and the BMC_{05}s were calculated as the concentration C that satisfies

$$\frac{P(C) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the model fits. The degrees of freedom for this test are equal to k minus the number of q_i's whose estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit. Resulting BMC_{05}s were adjusted for the non-constant exposure pattern by multiplying by 6/24 × 5/7.

Results from the model fitting, along with the raw BMC_{05}s and their 95% lower confidence limits (LCLs), are displayed in Table 7. Plots are shown in Figure 2. The highest dose group was dropped for forestomach ulcers in male mice because it exhibited downturn. None of the fitted models showed a significant lack of fit.

BMC_{05}s for these non-cancer endpoints range from 0.89 ppm (4.3 mg/m^3) (95% LCL = 0.73 ppm [3.5 mg/m^3]) for hyperplasia of the forestomach epithelium in female mice to 16.5 ppm (80 mg/m^3) (95% LCL = 10.9 ppm [53 mg/m^3]) for Kupffer cell pigmentation in male mice. In concordance with the greater sensitivity of rats than mice to 2-butoxyethanol-induced hemolysis, lower BMC_{05} values were determined for Kupffer cell pigmentation in rats.

A TC was developed on the basis of the lower end of the range of the BMC_{05}s for these effects (i.e., that for hyperplasia of the forestomach epithelium in female mice), although the range of these values is relatively small. In addition, hemosiderin pigmentation is considered to be secondary to hemolysis, rather than an adverse effect directly associated with exposure to 2-butoxyethanol. The TC was developed as follows:

$$\text{TC} = \frac{4.3 \text{ mg/m}^3}{100}$$

$$\cong 0.04 \text{ mg/m}^3$$

where:

- 4.3 mg/m^3 is the BMC associated with a 5% increase in the incidence of hyperplasia of the forestomach epithelium in female B6C3F$_1$ mice exposed to 2-butoxyethanol for 2 years (NTP, 1998), and
- 100 is the uncertainty factor (×10 for intraspecies variation and ×10 for interspecies variation). Available data are insufficient as a basis to replace default values for intra- and interspecies variations in toxicokinetics and toxicodynamics by compound-specific adjustments – i.e., the putatively toxic metabolite in the induction of local irritant effects is unknown, and relative sensitivity has not been investigated.

TABLE 7 BMC_{05}s and model fitting information for other non-hematological endpoints

	BMC_{05} (ppm)	95% LCL (ppm)	Chi-square	df	p-value
Kupffer cell pigmentation (male rats)	1.1	0.68	0.05	1	0.82
Kupffer cell pigmentation (female rats)	2.2	0.68	1.44	1	0.23
Forestomach ulcer (male mice)[1]	12.4	5.8	0.35	1	0.55
Hyperplasia of forestomach epithelium (male mice)	3.9	3.0	0.97	2	0.61
Forestomach ulcer (female mice)	4.3	3.2	0.001	1	0.91
Hyperplasia of forestomach epithelium (female mice)	0.89	0.73	4.05	2	0.13
Kupffer cell pigmentation (male mice)	16.5	10.9	1.84	1	0.17
Kupffer cell pigmentation (female mice)	6.6	2.9	1.77	2	0.41

[1] Highest dose group excluded to eliminate downturn from dose–response relationship.

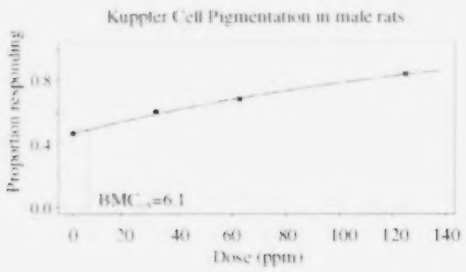
This TC for forestomach lesions is considered to be protective for squamous cell papillomas or carcinomas of the forestomach in mice for which tumorigenic potencies have been estimated using multistage modelling (Global82; Howe and Crump, 1982). TCs derived on the basis of the incidence of tumours at other sites, although the weight of evidence for an association with 2-butoxyethanol is considered quite limited, are greater than those for tumours of the forestomach.

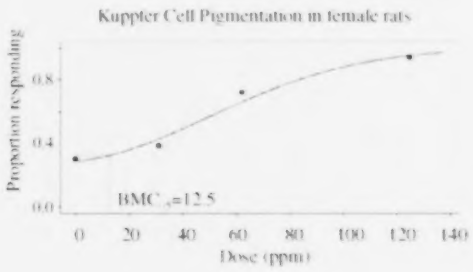
It is noteworthy that the TC based on forestomach lesions is 275-fold lower than that derived for 2-butoxyethanol-induced hematological effects. However, it is important to keep in mind that the BMC_{05}s for non-neoplastic lesions in the forestomach were derived on the basis of the incidences of lesions of all severities (combined), including those considered to be minimal, although if lesions of minimal severity were excluded, the resulting BMC_{05}s would be within 3-fold of those presented here. In addition, the association between exposure to 2-butoxyethanol and hemolysis has been much more thoroughly investigated than the association with effects on the forestomach, with some evidence (albeit quite weak) of hematological effects in humans.

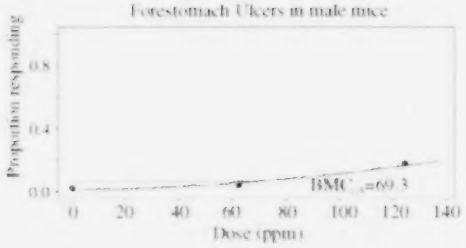
3.3.4 Risk characterization

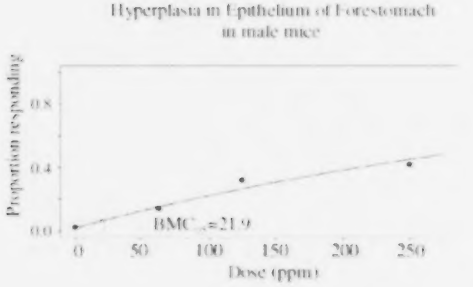
As discussed above, based on the limited data available on levels of 2-butoxyethanol in environmental media, inhalation in air appears to be a principal route of exposure to 2-butoxyethanol for the general population in Canada. The mean concentration of 2-butoxyethanol in outdoor air reported in the multimedia exposure study was 8.4 $\mu g/m^3$, with a maximum of 243 $\mu g/m^3$. However, as discussed below, the confidence in these values is low, due to the analytical methodology employed, although they are considered conservative. Indeed, in the only other Canadian study identified (in which the confidence is greater), the maximum outdoor air concentration reported near a likely source (an automotive plant) was lower (i.e., 7.3 $\mu g/m^3$). Exposure in indoor air is generally greater than that in outdoor air. In the multimedia exposure study, the mean concentration of 2-butoxyethanol in 50 samples from Canadian residences was 27.5 $\mu g/m^3$, with a maximum measured concentration of 438 $\mu g/m^3$. However, exposure to 2-butoxyethanol through use of some consumer products could be much higher. For example, conservative estimates of short-term indoor air concentrations resulting from emissions of some common household products recently

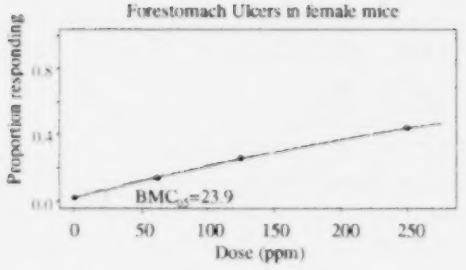
FIGURE 2 Exposure-response curves for non-haematological effects in mice and rats

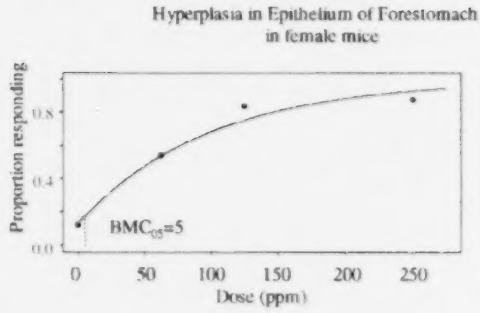


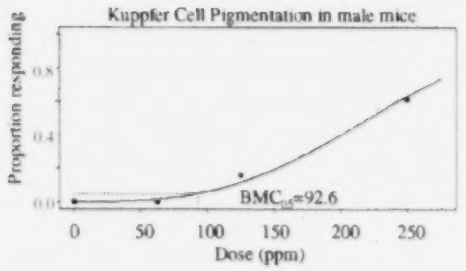


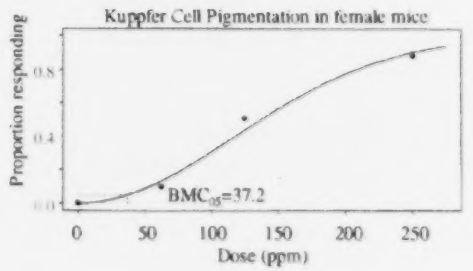












* BMC_{05} unadjusted for non-constant dosing

investigated in Canada range up to 62 mg/m^3 (62 000 µg/m^3). Intake of 2-butoxyethanol via inhalation and dermal exposure through use of such consumer products was estimated to be much greater than intake from background environmental sources.

Based on evaluation of available data (principally toxicological investigations in experimental animals), hematotoxicity is considered the principal effect for characterization of potential risk to humans associated with exposure to 2-butoxyethanol. As described above, a TC of 11 mg/m^3 (11 000 µg/m^3) was derived for 2-butoxyethanol on the basis of BMCs determined for alterations in hematological parameters based on observations in rats and mice following long-term exposure, taking into consideration interspecies differences in toxicokinetics and toxicodynamics. A more conservative TC of 0.04 mg/m^3 (40 µg/m^3) was also derived for co-critical forestomach lesions reported in chronically exposed mice, although confidence in this latter value is less, for the reasons outlined in Section 3.3.5.

Comparison of measured exposure levels in outdoor air with the TCs indicates that average exposure in the ambient environment does not exceed either the TC for hematological effects (in which there is greater confidence) or the more conservative TC for lesions of the forestomach. Likewise, mean concentrations in indoor air reported in the multimedia exposure study are less than the TCs. However, maximum concentrations reported in outdoor and indoor air in the multimedia exposure study exceed the more conservative TC for forestomach lesions.

The elevated exposure in indoor air is likely due to use of consumer products containing 2-butoxyethanol. Indeed, crude estimates of exposure through direct use of such products, although based on limited data, greatly exceed the TCs for adverse health effects. The maximum estimated short-term indoor air concentration of 2-butoxyethanol based on monitored emissions from a few common household products is about 1550-fold greater than the more conservative TC for forestomach lesions; this predicted indoor air concentration resulting from emissions from consumer products is also 6-fold greater than and the TC in which confidence is greater (i.e., hematological effects).

3.3.5 Uncertainties and degree of confidence in the human health risk characterization

There is a high degree of uncertainty in the estimates of population exposure that have been developed for this assessment primarily as a basis for determining principal media of exposure, due to the paucity of data on levels of 2-butoxyethanol in environmental media. Although estimates of average exposures were based on data reported in the multimedia exposure study conducted in Canada, the methodology employed in this study is considered experimental, and confidence in the results is low. For example, recovery was relatively low (i.e., 52% in air), and concentrations in "blanks" were high and variable, perhaps due in part to the use of non-standard desorbing solvents to extract 2-butoxyethanol from these samples. However, while likely conservative, the range of concentrations is similar to the single reported value for residential indoor air outside Canada. These estimates also do not take into account intake via dermal absorption of airborne 2-butoxyethanol, which, although less than the amount inhaled from indoor air, could be significant. In addition, there is a moderate degree of uncertainty concerning the relative contribution of food to total intake of 2-butoxyethanol, as no relevant monitoring data were identified, and this might be an appropriate area of additional investigation.

Confidence in the estimates of exposure to 2-butoxyethanol through use of products containing the substance is low to moderate for those few substances for which measured emissions permitted development of such estimates. For example, a conservative room ventilation rate of 0.5 air change per hour was

incorporated into the calculations of indoor air concentrations resulting from typical use of spray cleaning products; if a higher rate of 1.0 air change per hour were applied, concentrations in indoor air resulting from the use of these products would be about 2-fold lower. Conversely, the estimates of dermal uptake of 2-butoxyethanol were based on a non-steady-state approach; these estimates are up to an order of magnitude lower than they would be if other, more conservative approaches were adopted. However, in spite of these uncertainties, confidence in these estimates based on measured emissions is greater than confidence in estimates that could be derived on the basis of product composition data. The inhalation and dermal exposures estimated in this assessment are for the average durations and frequencies of performance of specific tasks. However, based on the 95th percentiles reported in U.S. EPA (1997), a significant fraction of the population performs some of these tasks on a daily basis and for roughly three to four times as long as the durations assumed here, and they would have correspondingly greater exposures. It should also be noted that the values presented here were based on extrapolation of emission factors for only a few of the potentially large number of products containing 2-butoxyethanol available to the consumer and, therefore, may significantly underestimate overall exposure associated with use of numerous products containing this glycol ether on a regular basis in the home. Acquisition of additional data on the content of 2-butoxyethanol in consumer products currently available in Canada and its emissions from these products is considered to be a high priority.

There is a moderate degree of certainty that hematotoxicity is the principal critical endpoint for 2-butoxyethanol, based on the observations in short- and long-term studies in multiple species of experimental animals. However, there is only limited evidence that 2-butoxyethanol induces hematological effects in humans; in fact, available data from *in vitro* investigations suggest that humans may be less sensitive than rats, which appear to be the most sensitive laboratory species identified to date. This lesser sensitivity of humans compared with rats with respect to hematological effects is accounted for in the small uncertainty factor applied to the BMC_{05} in the derivation of the TC, and limited available data from studies in humans indicated that the TC is protective. The component for interspecies toxicokinetics of the total compound-specific adjustment/uncertainty factor was based on data for a limited number of time points. However, the database for the component that has greater impact on deviation from default for the uncertainty factor (i.e., that of interspecies variations in dynamics) is much more extensive.

However, it should be noted that no data were available on the effects of 2-butoxyethanol on hematological parameters in rodents in the critical studies past 12 months. In addition, the sizes of the groups of animals in which blood was examined at each time point were small. Although the subchronic study conducted by the NTP (1998) involved a greater number of exposure levels, because of the high concentrations, modelling of these data would not improve characterization of exposure–response in the region of the BMC_{05}s.

The TC was derived on the basis of point estimates for the BMCs, as opposed to the 95% LCLs; however, use of the LCLs would not change the TC substantially, since for most parameters, the LCL was less than 3-fold lower than the midpoint estimate. In addition, if the BMCs for hematological effects had been determined on the basis that 10% of the control population was considered "abnormal" (as opposed to 5% used in derivations presented), the resulting values would vary by less than 1.5-fold.

There is a moderate to high amount of uncertainty concerning the TC derived on the basis of the BMC for lesions of the forestomach in mice (although these effects were consistently observed in subchronic studies in rats and mice and in the only chronic study in mice). Although the profile of effects suggests a progression from irritation to ulceration and tumour formation,

due to the lack of information on the mode of induction of these lesions, including the nature of delivery to the target site and the role of putatively toxic metabolites, their relevance to humans is unknown but cannot be precluded. (It is noteworthy that, in the only relevant clinical trials in humans, irritation of the eyes and upper respiratory tract was the most sensitive effect reported.) If these lesions are local effects resulting from ingestion, mice are likely to be considerably more sensitive due to longer residence time in the forestomach (and its low acidity) compared with the human esophagus. Because the animals were exposed to 2-butoxyethanol via inhalation, preening may have contributed to exposure at the target site. If ingestion via preening or mucociliary clearance were significant, then the TC based on BMCs derived on the basis of the airborne exposure concentrations would likely overestimate the risk to humans (i.e., there would not be the additional exposure via ingestion). On the other hand, dermal absorption of airborne 2-butoxyethanol by humans (which could be significant, i.e., up to 27% of total uptake, based on clinical investigations in humans; Corley *et al.*, 1997) has also not been considered in the determination of the TC. In addition, the BMC_{05}s upon which the TC is based were derived on the basis of inclusion of forestomach lesions of all severities combined; if lesions of minimal severity were excluded, the resulting BMC_{05}s would be within 3-fold of the values presented here.

There is also some uncertainty associated with the characterization of risk in that the TCs derived on the basis of long-term studies in rodents are compared with estimates of short-term exposure associated with use of a small number of consumer products containing 2-butoxyethanol. However, although estimated exposures were based on average use patterns, a proportion of the general population uses these products more frequently (up to 22 times more) and for longer duration (up to 4-fold longer) than average (U.S. EPA, 1997). As well, as noted above, several products containing the substance may be used throughout the day, thereby potentially increasing the magnitude and duration of exposure. In addition, hematological effects, similar to those observed in the chronic bioassay, have been reported in acute and short-term studies in experimental animals, indicating that prolonged exposure is not requisite for induction of hematotoxicity by 2-butoxyethanol. Thus, it was considered appropriate to characterize risk on the basis of these data.

3.4 Conclusions

CEPA 1999 64(a): Based on conservative estimates of exposure and effects in Canada, risk quotients for terrestrial wildlife, soil organisms and aquatic organisms are less than one. The environmental risks associated with estimated concentrations of 2-butoxyethanol likely to be found in Canada therefore appear to be low. Therefore, available data indicate that it is unlikely that 2-butoxyethanol is entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, and it is not considered to be "toxic" as defined in CEPA 1999 Paragraph 64(a).

CEPA 1999 64(b): 2-Butoxyethanol is not involved in the depletion of stratospheric ozone and likely does not contribute significantly to climate change. Because of its very low estimated concentration in air in Canada, it is unlikely to play a significant role in tropospheric ozone

production. Therefore, based on available data, it has been concluded that 2-butoxyethanol is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends, and it is not considered to be "toxic" as defined in CEPA 1999 Paragraph 64(b).

CEPA 1999 64(c): Based on available data, 2-butoxyethanol is considered to be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, 2-butoxyethanol is considered to be "toxic" as defined in CEPA 1999 Paragraph 64(c).

Overall conclusion: Based on critical assessment of relevant information, 2-butoxyethanol is considered to be "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

Additional characterization of the ranges and distributions of concentrations of 2-butoxyethanol in consumer products currently available in Canada and their emissions is considered a clear priority as a basis for risk management.

4.0 REFERENCES

Aasmoe, L., J.-O. Winberg and J. Aarbakke. 1998. The role of liver alcohol dehydrogenase isoenzymes in the oxidation of glycolethers in male and female rats. Toxicol. Appl. Pharmacol. 150: 86–90.

Agarwal, D.P and H.W. Goedde. 1992. Pharmacokinetics of alcohol dehydrogenase. *In*: W. Kalow (ed.), Pharmacokinetics of drug metabolism. Pergamon Press. pp. 263–280.

Allan, M. 1995. Probabilistic assessment of 24-hour breathing rates. Final report. Prepared for Health Protection Branch, Health Canada, Ottawa, Ontario. Cornerstone Engineering and Consulting Inc., Calgary, Alberta. October 1995.

ASTER (Assessment Tools for the Evaluation of Risk). 1996. ASTER ecotoxicity profile. National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Duluth, Minnesota.

Atkins, H.L. 1999. Personal communication (letter dated March 25, 1999). Bone Marrow Transplantation and Cancer Research, Ottawa Hospital, General Campus, Ottawa, Ontario.

ATSDR (Agency for Toxic Substances and Disease Registry). 1998. Toxicological profile for 2-butoxyethanol and 2-butoxyethanol acetate. U.S. Department of Health and Human Services, Atlanta, Georgia.

Bartnik, F.G., A.K. Reddy, G. Klecak, V. Zimmermann, J.J. Hostynek and K. Kunstler. 1987. Percutaneous absorption, metabolism, and hemolytic activity of n-butoxyethanol. Fundam. Appl. Toxicol. 8: 59–70.

Bauer, P., M. Weber, J.M. Mur, J.C. Protois, P.E. Bollaert, A. Condi, A. Larcan and H. Lambert. 1992. Transient non-cardiogenic pulmonary edema following massive ingestion of ethylene glycol butyl ether. Intensive Care Med. 18: 250–251.

Beihoffer, J. and C. Ferguson. 1994. Determination of selected carboxylic acids and alcohols in groundwater by GC–MS. J. Chromatogr. Sci. 32: 102–106.

Biospherics Inc. 1981a. The acute toxicity of Wellaid 791 [2-butoxyethanol] to the grass shrimp, *Palaemonetes pugio*. Report prepared for Standard Oil Company by Biospherics Inc., Rockville, Maryland. 7 pp. (Project No. 81-3-9689 GS).

Biospherics Inc. 1981b. The acute toxicity of Wellaid 791 [2-butoxyethanol] to the mummichog, *Fundulus heteroclitus*. Report prepared for Standard Oil Company by Biospherics Inc., Rockville, Maryland. 7 pp. (Project No. 81-3-9689 M).

Bringmann, G. and R. Kuehn. 1978. Testing of substances for their toxicity threshold: model organisms *Microcystis* (*Diplocystis*) *aeruginosa* and *Scenedesmus quadricauda*. Mitt. Int. Ver. Theor. Angew. Limnol. 21: 275–284.

Brinke, J.T. 1995. Development of new VOC exposure metrics and their relationship to "sick building syndrome" symptoms. Ph.D. thesis, University of California, Berkeley, California. August 1995.

Brown, K.W. and K.C. Donnelly. 1988. An estimation of the risk associated with the organic constituents of hazardous and municipal waste landfill leachates. Hazard. Waste Hazard. Mater. 5: 1–30.

Bunce, N. 1996. Atmospheric properties of substances on the Priority Substances List #2 (PSL2). Report to Environment Canada. University of Guelph, Guelph, Ontario. 13 pp.

Canadian Chemical Producers' Association. 1997. Reducing emissions 4. A Responsible Care initiative. 1995 emissions inventory and five year projections. Ottawa, Ontario.

Canadian Chemical Producers' Association. 1999a. Reducing emissions 6. A Responsible Care initiative. 1997 emissions inventory and five year projections. Ottawa, Ontario.

Canadian Chemical Producers' Association. 1999b. Reducing emissions 7. A Responsible Care initiative. 1998 emissions inventory and five year projections. Ottawa, Ontario.

Cao, X.L. 1999. Emissions of glycol ethers from consumer products — a final report for 1998/1999 CEPA project. Health Canada, Ottawa, Ontario. June 1999.

Carpenter, C.P. and H.F. Smyth, Jr. 1946. Chemical burns of the rabbit cornea. Am. J. Ophthalmol. 29: 1363–1372.

Carpenter, C.P., U.C. Pozzani, C.S. Weil, J.H. Nair, G.A. Keck and H.F. Smyth, Jr. 1956. The toxicity of butyl cellosolve solvent. Arch. Ind. Health 14: 114–131.

Castle, L., C.P. Offen, M.J. Baxter and J. Gilbert. 1997. Migration studies from paper and board food packaging materials. 1. Compositional analysis. Food Addit. Contam. 14(1): 35–44.

ChemCAN4. 1996. Level III fugacity model of the regional fate of chemicals. Version 0.95, May 1996. Developed by D. Mackay, A. DiGuardo, S. Paterson and D.D. Tam, University of Toronto, Toronto, Ontario (www.trentu.ca/cemc/ChemCAN.html).

Chiewchanwit, T. and W.W. Au. 1995. Mutagenicity and cytotoxicity of 2-butoxyethanol and its metabolite, 2-butoxyacetaldehyde, in Chinese hamster ovary (CHO-AS52) cells. Mutat. Res. 334: 341–346.

CIBA-GEIGY Corp. 1979. 96-hour acute toxicity to bluegill sunfish (*Lepomis macrochirus*). Report prepared for CIBA-GEIGY Corp. by EN-CAS Analytical Laboratories, Winston-Salem, North Carolina. 6 pp. (Report No. E-8566).

Ciccioli, P., E. Brancaleoni, A. Cecinato, R. Sparapani and M. Frattoni. 1993. Identification and determination of biogenic and anthropogenic volatile organic compounds in forest areas of northern and southern Europe and a remote site of the Himalaya region by high-resolution gas chromatography–mass spectrometry. J. Chromatogr. 643: 55–69.

Ciccioli, P., A. Cecinato, E. Brancaleoni, M. Frattoni, F. Bruner and M. Maione. 1996. Occurrence of oxygenated volatile organic compounds (VOC) in Antarctica. Int. J. Environ. Anal. Chem. 62: 245–253.

CMA (Chemical Manufacturers' Association). 1983. 90-day subchronic dermal toxicity study in rabbits with ethylene glycol monobutyl ether. Washington, D.C. [cited in Tyler, 1984].

Collinot, J.P., J.C. Collinot, F. Deschamps, D. Decolin, G. Siest and M.M. Galteau. 1996. Evaluation of urinary D-glucaric acid excretion in workers exposed to butyl glycol. J. Toxicol. Environ. Health 48: 349–358.

Conor Pacific Environmental Technologies Inc. 1998. A report on multimedia exposures to selected PSL2 substances. Prepared on contract for Health Canada (Project No. 741-6705).

Corley, R.A., G.A. Bormett and B.I. Ghanayem. 1994. Physiologically based pharmacokinetics of 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in rats and humans. Toxicol. Appl. Pharmacol. 129: 61–79.

Corley, R.A., D.A. Markham, C. Banks, P. Delorme, A. Masterman and J.M. Houle. 1997. Physiologically based pharmacokinetics and the dermal absorption of 2-butoxyethanol vapour by humans. Fundam. Appl. Toxicol. 39: 120–130.

Crump, K. 1995. Calculation of benchmark doses for continuous data. Risk Anal. 15: 79–89.

Crump, K.S. and C. Van Landingham. 1996. BENCH_C: A Fortran program to calculate benchmark doses from continuous data. ICF Consulting, Ruston, Louisiana.

Daisey, J.M., A.T. Hodgeson, W.J. Fisk, M.J. Mendell and J. Ten Brinke. 1994. Volatile organic compounds in twelve California office buildings: classes, concentrations and sources. Atmos. Environ. 28(22): 3557–3562.

Dean, B.S. and E.P. Krenzelok. 1992. Clinical evaluation of pediatric ethylene glycol monobutyl ether poisonings. Clin. Toxicol. 30: 557–563.

De Bortoli, M., H. Knöppel, E. Pecchio, A. Peil, L. Rogora, H. Schauenburg, H. Schlitt and H. Vissers. 1986. Concentrations of selected organic pollutants in indoor and outdoor air in northern Italy. Environ. Int. 12: 343–350.

Dieter, M.P., C.W. Jameson, R.R. Maronpot, R. Langenbach and A.G. Braun. 1990. The chemotherapeutic potential of glycol alkyl ethers: structure–activity studies of nine compounds in a Fischer-rat leukemia transplant model. Cancer Chemother. Pharmacol. 26: 173–180.

Dill, J.A., K.M. Lee, D.J. Bates, D.J. Anderson, R.E. Johnson, B.J. Chou, L.T. Burka and J.H. Roycroft. 1998. Toxicokinetics of inhaled 2-butoxyethanol and its major metabolite, 2-butoxyacetic acid, in F344 rats and B6C3F1 mice. Toxicol. Appl. Pharmacol. 153: 227–242.

DMER (Don Mackay Environmental Research) and AEL (Angus Environmental Limited). 1996. Pathways analysis using fugacity modeling of 2-butoxyethanol for the second Priority Substances List. Report prepared for Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, by DMER, Peterborough, Ontario, and AEL, Don Mills, Ontario. March 1996.

Dodd, D.E., W.M. Snellings, R.R. Maronpot and B. Ballantyne. 1983. Ethylene glycol monobutyl ether: acute, 9-day, and 90-day vapor inhalation studies in Fischer 344 rats. Toxicol. Appl. Pharmacol. 68: 405–414.

Doe, J.E. 1984. Further studies on the toxicology of the glycol ethers with emphasis on rapid screening and hazard assessment. Environ. Health Perspect. 57: 199–206.

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals). 1995. The toxicology of glycol ethers and its relevance to man. Brussels, August 1995 (Technical Report No. 64).

EHD (Environmental Health Directorate). 1998. Exposure factors for assessing total daily intake of Priority Substances by the general population of Canada. Unpublished report. Priority Substances Section, Environmental Health Directorate, Ottawa, Ontario. Draft, March 1998.

Elias, Z., M.C. Danière, A.M. Marande, O. Poirot, F. Terzetti and O. Schneider. 1996. Genotoxic and/or epigenetic effects of some glycol ethers: results of different short-term tests. Occup. Hyg. 2: 187–212.

Environment Canada. 1997a. Environmental assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance manual version 1.0 — March 1997. Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Hull, Quebec (EPS 2/CC/3E).

Environment Canada. 1997b. Results of the CEPA Section 16 Notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. Use Patterns Section, Commercial Chemicals Evaluation Branch, Hull, Quebec.

Environment Canada. 1997c. Notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. *Canada Gazette*, Part I, February 15, 1997, pp. 366–368.

Environment Canada. 1999. *Canadian Environmental Protection Act* — Priority Substances List — Supporting document for the environmental assessment of 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol. Commercial Chemicals Evaluation Branch, Hull, Quebec.

Environment Canada and Health Canada. 2000. Publication after Assessment of a substance — 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol — Specified on the Priority Substances List (Subsection 77(1) of the *Canadian Environmental Protection Act, 1999*). *Canada Gazette*, Part I, August 19, 2000, pp. 2622-2626.

Exon, J.H., G.G. Mather, J.L. Bussiere, D.P. Olson and P.A. Talcott. 1991. Effects of subchronic exposure of rats to 2-methoxyethanol or 2-butoxyethanol: thymic atrophy and immunotoxicity. Fundam. Appl. Toxicol. 16: 830–840.

Flick, E.W. 1986. Household and automotive cleaners and polishes. 3rd ed. Noyes Publications, Park Ridge, New Jersey.

Flick, E.W. 1989. Advanced cleaning product formulations: household, industrial, automotive. Vol. 1. Noyes Publications, Park Ridge, New Jersey.

General Paint Ltd. 1997. Material Safety Data Sheets for product codes 97-530, 79-905, 71-030. Published on www.generalpaint.com/msds, last updated December 22, 1997.

Ghanayem, B.I. 1989. Metabolic and cellular basis of 2-butoxyethanol-induced hemolytic anemia in rats and assessment of human risk *in vitro*. Biochem. Pharmacol. 38: 1679–1684.

Ghanayem, B.I. 1996. An overview of the hematotoxicity of ethylene glycol ethers. Occup. Hyg. 2: 253–268.

Ghanayem, B.I. and C.A. Sullivan. 1993. Assessment of the haemolytic activity of 2-butoxyethanol and its major metabolite, butoxyacetic acid, in various mammals including humans. Hum. Exp. Toxicol. 12(4): 305–311.

Ghanayem, B.I., P.C. Blair, M.B. Thompson, R.R. Maronpot and H.B. Matthews. 1987. Effect of age on the toxicity and metabolism of ethylene glycol monobutyl ether (2-butoxyethanol) in rats. Toxicol. Appl. Pharmacol. 91: 222–234.

Ghanayem, B.I., I.M. Sanchez and H.B. Matthews. 1992. Development of tolerance to 2-butoxyethanol-induced hemolytic anemia and studies to elucidate the underlying mechanisms. Toxicol. Appl. Pharmacol. 112: 198–206.

Gijsenbergh, F.P., M. Jenco, H. Veulemans, D. Groeseneken, R. Verberckmoes and H.H. Delooz. 1989. Acute butylglycol intoxication: a case report. Hum. Toxicol. 8: 243–245.

Goedde, H.W. and D.P. Agarwal. 1992. Pharmacokinetics of aldehyde dehydrogenase. *In*: W. Kalow (ed.), Pharmacokinetics of drug metabolism. Pergamon Press. pp. 281–311.

Gollapudi, B.B., E.D. Barber, T.E. Lawlor and S.A. Lewis. 1996. Re-examination of the mutagenicity of ethylene glycol monobutyl ether to *Salmonella* tester strain TA97a. Mutat. Res. 370: 61–64.

Grant, D., S. Sulsh, H.B. Jones, S.D. Gangolli and W.H. Butler. 1985. Acute toxicity and recovery in the hemopoietic system of rats after treatment with ethylene glycol monomethyl and monobutyl ethers. Toxicol. Appl. Pharmacol. 77: 187–200.

Grant, D.M., R.A. Corley and K.D. Thrall. 1997. A comparison of gender, age and species differences in renal active secretion of 2-butoxyacetic acid. Presented at 8th Annual North American ISSX Meeting, Hilton Head, South Carolina, October 26–30, 1997. International Society for the Study of Xenobiotics.

Guy, R.H. and R.O. Potts. 1993. Penetration of industrial chemicals across the skin: a predictive model. Am. J. Ind. Med. 23: 711–719.

Hardin, B.D., P.T. Goad and J.R. Burg. 1984. Developmental toxicity of four glycol ethers applied cutaneously to rats. Environ. Health Perspect. 57: 69–74.

Haufroid, V., F. Thirion, P. Mertens, J.P. Buchet and D. Lison. 1997. Biological monitoring of workers exposed to low levels of 2-butoxyethanol. Int. Arch. Occup. Environ. Health 70: 232–236.

Health Canada. 1994. *Canadian Environmental Protection Act* — Human health risk assessment for Priority Substances. Environmental Health Directorate, Ottawa, Ontario.

Health Canada. 1998a. Personal communication on glycol ethers in consumer products from P. Chowhan, Product Safety Bureau, Ottawa, Ontario.

Health Canada. 1998b. Personal communication on glycol ethers in pesticides from V. Bergeron, Pest Management Regulatory Agency, Ottawa, Ontario.

Health Canada. 2001. Supporting documentation for Priority Substances Assessment Report on 2-butoxyethanol. Existing Substances Division, Healthy Environments and Consumer Safety Branch, Ottawa, Ontario.

Health Canada Cosmetic Notification System. 2001. Search of Health Canada Cosmetic Notification System database, March 20, 2001. Product Safety Bureau, Health Canada, Ottawa, Ontario.

Heindel, J.J., D.K. Gulati, V.S. Russell, J.R. Reel, A.D. Lawton and J.C. Lamb IV. 1990. Assessment of ethylene glycol monobutyl and monophenyl ether reproductive toxicity using a continuous breeding protocol in Swiss CD-1 mice. Fundam. Appl. Toxicol. 15: 683–696.

Hoflack, J.C., L. Lambolez, Z. Elias and P. Vasseur. 1995. Mutagenicity of ethylene glycol ethers and of their metabolites in *Salmonella typhimurium* his . Mutat. Res. 341: 281–287.

Howard, P.H. 1993. Handbook of environmental fate and exposure data for organic chemicals. Vol. IV. Solvents 2. Lewis Publishers, Chelsea, Michigan. 280 pp.

Howard, P.H., R.S. Boethling, W.F. Jarvis, W.M. Meylan and E.M. Michalenko. 1991. Handbook of environmental degradation rates. Lewis Publishers, Chelsea, Michigan.

Howe, R.B. 1995. THRESH: A computer program to compute a reference dose from quantal animal toxicity data using the benchmark dose method. KCF Kaiser Engineers, Inc., Ruston, Louisiana.

Howe, R.B. and K.S. Crump. 1982. Global82: A computer program to extrapolate quantal animal toxicity data to low doses. Science Research Systems, Ruston, Louisiana.

IPCS (International Programme on Chemical Safety). 1998. 2-Butoxyethanol. World Health Organization, Geneva (Concise International Chemical Assessment Document 10).

Jacobs, G.A. 1992. Eye irritation tests on two ethylene glycol ethers. J. Am. Coll. Toxicol. 11: 738.

Jacobs, G.A., A. Castellazzi and P.J. Dierickx. 1989. Evaluation of a non-invasive human and an *in vitro* cytotoxicity method as alternatives to the skin irritation test on rabbits. Contact Dermatitis 21: 239-244.

Jay, K. and L. Stieglitz. 1995. Identification and quantification of volatile organic components in emissions of waste incineration plants. Chemosphere 30: 1249–1260.

Johanson, G. 1986. Physiologically based pharmacokinetic modeling of inhaled 2-butoxyethanol in man. Toxicol. Lett. 34: 23–31.

Johanson, G. 1988. Toxicokinetics of 2-butoxyethanol. Uptake, distribution, metabolism, and excretion in man and laboratory animals. National Institute of Occupational Health, Solna, Sweden. 78 pp. (Arbete Och Halsa 3).

Johanson, G. and P. Fernström. 1988. Influence of water on the percutaneous absorption of 2-butoxyethanol in guinea pigs. Scand. J. Work Environ. Health 1: 95–100.

Johanson, G. and S. Johnsson. 1991. Gas chromatographic determination of butoxyacetic acid in human blood after exposure to 2-butoxyethanol. Arch. Toxicol. 65: 433–435.

Kane, D.M. 1993. Evaluation of ChemCAN2 — a fugacity-based multimedia exposure model used to predict the environmental fate of organic chemicals in Canada. Draft report, January 14, 1993. 28 pp.

Keith, G., C. Coulais, A. Edorh, M.C. Bottin and B. Rihn. 1996. Ethylene glycol monobutyl ether has neither epigenetic nor genotoxic effects in acute treated rats and in subchronic treated v-HA-*ras* transgenic mice. Occup. Hyg. 2: 237–249.

Kennah, H.E. II, S. Hignet, P.E. Laux, J.D. Dorko and C.S.Barrow. 1989. An objective procedure for quantitating eye irritation based upon changes of corneal thickness. Fundam. Appl. Toxicol. 12: 258–268.

Kerckaert, G.A., R. Brauninger, R.A. LeBouef and R.J. Isfort. 1996. Use of the Syrian hamster embryo cell transformation assay for carcinogenicity prediction of chemicals currently being tested by the National Toxicology Program in rodent bioassays. Environ. Health Perspect. 104 (Suppl. 5): 1075–1084.

Krasavage, W.J. 1986. Subchronic oral toxicity of ethylene glycol monobutyl ether in male rats. Fundam. Appl. Toxicol. 6: 349–355.

Kvelland, I. 1988. The mutagenic effect of five oil dispersants and of ethylene glycol-monobutyl-ether in bacteriophage T4D. Hereditas 109: 149–150.

Lee, K.M., J.A. Dill, B.J. Chou and J.H. Roycroft. 1998. Physiologically based pharmacokinetic model for chronic inhalation of 2-butoxyethanol. Toxicol. Appl. Pharmacol. 153: 211–226.

Lyman, W.J., W.R. Feehl and D.H. Rosenblatt. 1990. Handbook of chemical property estimation methods — environmental behaviour of organic compounds. American Chemical Society, Washington, D.C.

Meek, M.E., R. Newhook, R.G. Liteplo and V.C. Armstrong. 1994. Approach to assessment of risk to human health for Priority Substances under the *Canadian Environmental Protection Act*. J. Environ. Sci. Health C12(2): 105–134.

Ministers' Expert Advisory Panel. 1995. Report of the Ministers' Expert Advisory Panel on the second Priority Substances List under the *Canadian Environmental Protection Act* (CEPA). Government of Canada, Ottawa, Ontario. 26 pp.

Morris, B.J., B.K. Shipp, T.A. Bartow and B.L. Blaylock. 1996. Oral exposure to 2-butoxyethanol alters immune response in BALB/c mice. Toxicologist 30 (1–2): 342 (Abstract 1756).

Nagano, K., E. Nakayama, M. Koyano, H. Oobayashi, H. Adachi and T. Yamada. 1979. [Testicular atrophy of mice induced by ethylene glycol mono alkyl ethers.] Jpn. J. Ind. Health 21: 29–35 (in Japanese, with English abstract and tables).

Nagano, K., E. Nakayama, M. Koyano, H. Oobayashi, T. Nishizawa, H. Okuda and K. Yamazaki. 1984. Experimental studies on toxicity of ethylene glycol alkyl ethers in Japan. Environ. Health Perspect. 57: 75–84.

National Industrial Chemicals Notification and Assessment Scheme. 1996. Priority Existing Chemicals, Chemical No. 6. 2-Butoxyethanol in cleaning product. Australian Government Publishing Service, Canberra.

Nisse, P., V. Coquelle-Couplet, X. Forceville and M. Mathieu-Nolf. 1998. Renal failure after suicidal ingestion of window cleaner. A case report. Vet. Hum. Toxicol. 40(3): 173.

Norbäck, D., G. Wieslander and C. Edling. 1995. Occupational exposure to volatile organic compounds (VOCs), and other air pollutants from the indoor application of water-based paints. Ann. Occup. Hyg. 39(6): 783–794.

Norbäck, D., G. Wieslander, C. Edling and G. Johanson. 1996. House painters' exposure to glycols and glycol ethers from water based paints. Occup. Hyg. 2: 111–117.

NTP (National Toxicology Program). 1989. Teratologic evaluation of ethylene glycol monobutyl ether (CAS No. 111-76-2) administered to Fischer-344 rats on either gestational days 9 through 11 or days 11 through 13. National Institutes of Health, Research Triangle Park, North Carolina (PB89-165849).

NTP (National Toxicology Program). 1993. NTP technical report on toxicity studies of ethylene glycol ethers 2-methoxyethanol, 2-ethoxyethanol, 2-butoxyethanol (CAS Nos. 109-86-4, 110-80-5, 111-76-2) administered in drinking water to F344/N rats and B6C3F$_1$ mice. National Institutes of Health, U.S. Department of Health and Human Services, Research Triangle Park, North Carolina. 122 pp. + appendices. (NTP Toxicity Report Series No. 26; NIH Publication 93-3349).

NTP (National Toxicology Program). 1998. Toxicology and carcinogenesis studies of 2-butoxyethanol (CAS No. 111-76-2) in F344/N rats and B6C3F$_1$ mice (inhalation studies). Draft technical report. National Institutes of Health, U.S. Department of Health and Human Services, Research Triangle Park, North Carolina (NTP TR 484).

OMEE (Ontario Ministry of Environment and Energy). 1994. Windsor Air Quality Study: TAGA 6000 survey results. Windsor Air Quality Committee. Queen's Printer for Ontario, Toronto, Ontario. Fall 1994 (PIBS 3152E; ISBN 0-7778-2831-6).

OMEE (Ontario Ministry of Environment and Energy). 1996. Personal communication (dated June 20, 1996) from J. McGrachan, Etobicoke, Ontario, to J. Sealy, Health Canada, Ottawa, Ontario, concerning concentration of 2-butoxyethanol in water samples.

Plehn, W. 1990. Solvent emission from paints. Proc. 5th Int. Conf. Indoor Air Qual. Climate 3: 563–568.

Potts, R.O. and R.H. Guy. 1992. Predicting skin permeability. Pharm. Res. 9: 663–669.

Rambourg-Schepens, M.O., M. Buffet, R. Bertault, M. Jaussaud, B. Journe, R. Fay and D. Lamiable. 1988. Severe ethylene glycol butyl ether poisoning. Kinetics and metabolic pattern. Hum. Toxicol. 7: 187–189.

Rogozen, M.B., H.E. Rich, M.A. Gutman and D. Grosjean. 1987. Evaluation of potential toxic air contaminants, Phase I. Final report. State of California Air Resources Board, Sacramento, California. December 23, 1987 (Contract A4-131-32).

Rohm and Haas Co. 1989. Acute skin and eye irritation toxicity reports (final report) with cover sheets and letter dated 081089 (EPA/OTS Document No. 86-890001526S) [cited in ECETOC, 1995].

Schuler, R.L., B.D. Hardin, R.W. Niemeier, G. Booth, K. Hazelden, V. Piccirillo and K. Smith. 1984. Results of testing fifteen glycol ethers in a short-term *in vivo* reproductive toxicity assay. Environ. Health Perspect. 57: 141–146.

Shields, H.C., D.M. Fleischer and C.J. Weschler. 1996. Comparisons among VOCs measured in three types of U.S. commercial buildings with different occupant densities. Indoor Air 6: 2–17.

SIDS (Screening Information Data Set). 1996. 2-Butoxyethanol. SIDS Initial Assessment Report for 5th SIDS Initial Assessment Meeting. Report prepared by Worksafe Australia National Occupational Health and Safety Commission for Organisation for Economic Co-operation and Development. 28 pp.

Singh, P., S. Zhao and B.L. Blaylock. 1998. Topical exposure to 2-butoxyethanol alters systemic immune responses in BALB/c mice. Toxicologist 42 (Part 1-S): 209 (Abstract 1029).

Sivarao, D.V. and H.M. Mehendale. 1995. 2-Butoxyethanol autoprotection is due to resilience of newly formed erythrocytes to hemolysis. Arch. Toxicol. 69: 526–532.

Smialowicz, R.J., W.C. Williams, M.M. Riddle, D.L. Andrews, R.W. Luebke and C.B. Copeland. 1992. Comparative immunosuppression of various glycol ethers orally administered to Fischer 344 rats. Fundam. Appl. Toxicol. 18: 621–627.

Smyth, H.F. Jr., C.P. Carpenter, C.S. Weil, U.C. Pozzani and J.A. Striegel. 1962. Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23: 95–107.

SRC (Syracuse Research Corporation). 1988. Syracuse Research Corporation calculated values. Syracuse, N.Y.

Stemmler, K., W. Mengon, D.J. Kinnison and J.A. Kerr. 1997. OH radical-initiated oxidation of 2-butoxyethanol under laboratory conditions related to the troposphere: product studies and proposed mechanism. Environ. Sci. Technol. 31: 1496–1504.

Truhaut, R., H. Dutertre-Catella, N. Phu-Lich and V.N. Huyen. 1979. Comparative toxicological study of ethylglycol acetate and butylglycol acetate. Toxicol. Appl. Pharmacol. 51: 117–127.

Tuazon, E.C., S.M. Aschmann and R. Atkinson. 1998. Products of the gas-phase reactions of the OH radical with 1-methoxy-2-propanol and 2-butoxyethanol. Environ. Sci. Technol. 32: 3336–3345.

Tyl, R.W., G. Millicovsky, D.E. Dodd, I.M. Pritts, K.A. France and L.C. Fisher. 1984. Teratologic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and New Zealand white rabbits following inhalation exposure. Environ. Health Perspect. 57: 47–68.

Tyler, T.R. 1984. Acute and subchronic toxicity of ethylene glycol monobutyl ether. Environ. Health Perspect. 57: 185–191.

Udden, M.M. 1994. Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: II. Resistance in red blood cells from humans with potential susceptibility. J. Appl. Toxicol. 14: 97–102.

Udden, M.M. 1996. Effects of butoxyacetic acid on human red cells. Occup. Hyg. 2: 283–290.

Udden, M.M. and C.S. Patton. 1994. Hemolysis and deformability of erythrocytes exposed to butoxyacetic acid, a metabolite of 2-butoxyethanol: I. Sensitivity in rats and resistance in normal humans. J. Appl. Toxicol. 14: 91–96.

Union Carbide. 1980. Butyl cellosolve: 9-day repeated dermal application to rabbits. Corporate Applied Toxicology, Union Carbide Corporation, South Charleston, West Virginia (Bushy Run Research Center Project Report 43-76) [cited in Tyler, 1984].

Union Carbide. 1989. Butyl cellosolve *in vitro* mutagenesis studies. 3-test battery with attachments, cover sheets and letter dated 060689. Union Carbide Corporation (EPA/OTS Document No. 86-890000946) [cited in ECETOC, 1995].

U.S. Department of Health and Human Services. 1990. Occupational exposure to ethylene glycol monobutyl ether and ethylene glycol monobutyl ether acetate. Criteria for a recommended standard. Cincinnati, Ohio. September 1990.

U.S. EPA (United States Environmental Protection Agency). 1979. Ice fog suppression using thin chemical films. National Technical Information Service, U.S. Department of Commerce, Springfield, Virginia, January 1979 (NTIS Report PB-294 275).

U.S. EPA (United States Environmental Protection Agency). 1984. Cited in SIDS, 1996 [no additional information available].

U.S. EPA (United States Environmental Protection Agency). 1992. Dermal exposure assessment: Principles and applications. Interim report. Exposure Assessment Group, Office of Health and Environmental Assessment, Washington, D.C. January 1992 (EPA/600/8-91/011B).

U.S. EPA (United States Environmental Protection Agency). 1997. Exposure factors handbook. Vol. III. Activity factors. Office of Research and Development, National Center for Environmental Assessment, Washington, D.C. August 1997 (EPA/600/P-95/002Fc).

Van Leeuwen, C.J., P.T.J. Van Der Zandt, T. Aldenberg, H.J.M. Verhaar and J.L.M. Hermens. 1992. Application of QSARs, extrapolation and equilibrium partitioning in aquatic effects assessment. I. Narcotic industrial pollutants. Environ. Toxicol. Chem. 11: 267–282.

Versar Inc. 1986. Standard scenarios for estimating exposure to chemical substances during use of consumer products. Vol. 1. Prepared on contract for Exposure Evaluation Division, Office of Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C. (EPA Contract No. 68-02-3968 dated September 1986).

Villalobos-Pietrini, R., S. Gómez-Arroyo, M. Altamirano-Lozano, P. Orozco and P. Ríos. 1989. Cytogenetic effects of some cellosolves. Rev. Int. Contam. Ambient. 5: 41–48.

Vincent, R., A. Cicolella, I. Subra, B. Rieger, P. Poirot and F. Pierre. 1993. Occupational exposure to 2-butoxyethanol for workers using window cleaning agents. Appl. Occup. Environ. Hyg. 8(6): 580–586.

Welsch, F. and D. Stedman. 1984. Inhibition of metabolic cooperation between Chinese hamster V79 cells by structurally diverse teratogens. Teratogen. Carcinogen. Mutagen. 4: 285–301.

Wier, P.J., S.C. Lewis and K.A. Traul. 1987. A comparison of developmental toxicity evident at term to postnatal growth and survival using ethylene glycol monoethyl ether, ethylene glycol monobutyl ether and ethanol. Teratogen. Carcinogen. Mutagen. 7: 55–64.

Yasuhara, A., H. Shiraishi, M. Tsuji and T. Okuno. 1981. Analysis of organic substances in highly polluted river water by mass spectrometry. Environ. Sci. Technol. 15: 570–573.

Zeiger, E., B. Anderson, S. Haworth, T. Lawlor and K. Mortelmans. 1992. *Salmonella* mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutagen. 19 (Suppl. 21): 2–141.

Zhu, J., X.-L. Cao and R. Beauchamp. 2001. Determination of 2-butoxyethanol emissions from selected consumer products and its application in assessment of inhalation exposure associated with cleaning tasks. Environ. Int. 26: 589–597.

Zissu D. 1995. Experimental study of cutaneous tolerance to glycol ethers. Contact Dermatitis 32: 74–77.

APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental assessment

Data relevant to the assessment of whether 2-butoxyethanol is "toxic" to the environment under CEPA 1999 were identified from existing review documents, published reference texts and on-line searches, conducted between January and May 1996, of the following databases: ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1990–1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1993, 1994, 1995, up to January 15, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of 2-butoxyethanol. Data obtained after September 30, 1999, were not considered in this assessment unless they were critical data received during the 60-day public review of the report (August 19 to October 18, 2000).

In addition, a survey of Canadian industry was carried out under the authority of Section 16 of CEPA (Environment Canada, 1997b,c). Targeted companies with commercial activities involving more than 1000 kg of 2-butoxyethanol were required to supply information on uses, releases, environmental concentrations, effects or other data that were available to them for 2-butoxyethanol.

Health assessment

In addition to studies included in the review prepared by BIBRA Toxicology International and relevant studies included in reports published by the International Programme on Chemical Safety (IPCS, 1998) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1998), recent data have been identified through searching the following databases beginning in August of 1996 using the chemical name or the CAS number for both 2-butoxyethanol and

2-butoxyethyl acetate: Canadian Research Index, DIALOG (Cancerlit, Environmental Bibliography, Waternet, Water Resources Abstracts, Enviroline, CAB Abstracts, Food Science and Technology Abstracts, Pollution Abstracts and NTIS), Medline, Toxline Plus and TOXNET (CCRIS [Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute], GENE-TOX [Genetic Toxicology, U.S. Environmental Protection Agency] and EMIC [Environmental Mutagen Information Center database, Oak Ridge National Laboratory]). Data acquired as of October 1999 were considered for inclusion in this report.

As well as these databases, officials at the Product Safety Bureau and Drugs Directorate of Health Canada, along with the Pest Management Regulatory Agency, were contacted to obtain information relevant to this assessment.